



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 [REDACTED]

- 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 [REDACTED]

City [REDACTED]

State [REDACTED]

Email [REDACTED]

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.

Anxiety

(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.

This petition includes new published evidence and scientific research findings supporting the request to add "Anxiety" as a qualifying condition that were not present in the "General Anxiety Disorder" petition. This petition should be reviewed and not rejected for its similarity to an earlier petition due to the new evidence published by the Minnesota Department of Health, the Massachusetts Department of Health and other peer-reviewed medical research attached and included.

The number one condition that medical cannabis patients report that cannabis alleviates symptoms is Anxiety. Cannabis helps patients with Anxiety more than it helps alleviate chronic pain. It is for this reason and the reasons below that Anxiety should be added to the list of qualifying debilitating medical conditions for which medical cannabis may be used. Anxiety is a debilitating condition that affects the whole person, including treatment of other conditions.

<https://www.mass.gov/report/massachusetts-department-of-public-health-marijuana-research>
(REF #77) <https://www.mass.gov/files/documents/2019/07/09/MBHS-full-report-final.pdf>
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 mood and or mental health 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.

In the 1999 National Academy of Sciences Institute of Medicine report on marijuana, the National Academy of Science found that thorough medical research shows that marijuana reduces anxiety for "many people".

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

(REF #99) <https://www.nap.edu/download/6376>

page 165

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.**

In a study of medical marijuana patients in Arizona, many patients reported significant relief levels of anxiety.

(REF #13) <https://www.ncbi.nlm.nih.gov/pubmed/26317379>

367 medical marijuana patients in Arizona were surveyed.

181 patients reported using medical marijuana to experience relief from Anxiety
General relief from Anxiety symptoms was 82.9% with medical marijuana,

Relief by medical marijuana compared to other medications was 79.3% for Anxiety
Less frequent use of other medications was 85.9% for Anxiety

Patients who suffer from Post Traumatic Stress Disorder find relief of anxiety with medical cannabis. PTSD is a qualifying condition in Hawaii and other states. It makes logical sense to allow people who do not have PTSD to gain relief of anxiety by adding anxiety to the list of qualifying conditions.

In a small percentage of people, medical cannabis can aggravate their anxiety. For the majority of people, cannabis reduces anxiety. This contraindication is similar to other anti-anxiety prescriptions, for whom a small percentage, their anxiety can be aggravated. This is not a reason to reject a qualifying condition, merely a reality of using any medication. Some epilepsy medicines make seizures worse or more frequent for example.

Marijuana is safer than all prescription medications and most of OTC medications. Cannabis has less side effects, and no severe, toxic or dangerous side effects compared to all of the prescription medications used to treat Anxiety.

<https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml>

For example Benzodiazepines commonly used as anti anxiety medications, are responsible for hundreds of deaths each year in the United States.

<https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>

<https://directorsblog.nih.gov/2014/04/10/anxiety-reduction-exploring-the-role-of-cannabinoid-receptors/>

Relief of anxiety and stress is one of the most common reasons that people give for using marijuana

Anti-Anxiety medication Ativan may be implicated in Soundgarden's lead singer Chris Cornell's suicide.

<http://www.rollingstone.com/culture/news/ativan-what-you-need-to-know-about-anxiety-pills-w483638>

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 #98) <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.

The Mayo Clinic website has assembled dosage information on Medical Marijuana.

<http://www.mayoclinic.org/drugs-supplements/marijuana/dosing/hrb-20059701>

In the latest petition to add Anxiety to Ohio's medical marijuana program, the New Jersey Department of Health's final decision on a petition to add anxiety in New Jersey was included.

(REF 96) [https://med.ohio.gov/Portals/0/Publications/Medical%20Marijuana%20Petitions%202019/0133%20-%20Anxiety%20\[Rosenberger\].pdf?ver=2020-01-28-104750-247](https://med.ohio.gov/Portals/0/Publications/Medical%20Marijuana%20Petitions%202019/0133%20-%20Anxiety%20[Rosenberger].pdf?ver=2020-01-28-104750-247)

(REF 97)

https://www.nj.gov/health/medicalmarijuana/documents/agency_decision_letters/MMP_FAD_conditions_012319.pdf

New Jersey's medical cannabis program is similar to Hawaii's medical cannabis program. With similar requirements for petitions to meet.

On July 5, 2016, the Department published the Request for Petitions in the New Jersey Register advising that from August 1, 2016 to August 31, 2016, it was accepting petitions to establish additional medical conditions as "debilitating" under the MMP. 43 NJR. 1395(a). The Request for Petitions stated that the Department was seeking petitions in accordance with the Act, which authorizes the Department to include additional debilitating medical conditions under the MMP.

In the Request for Petitions, the public was advised that submitted petitions were required to include the following information, pursuant to N.J.A.C. 8:64-53:

- (1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;
- (2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;
- (3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting, or otherwise severely impair the patient's ability to carry on activities of daily living;
- (4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;
- (5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and
- (6) Letters of support from physicians or other licensed health care professionals knowledgeable about the condition.

New Jersey found that Anxiety met the requirements and accepted Anxiety as a qualifying condition.

Anxiety

Based upon my independent review of the petitions, I am granting those seeking to add anxiety to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that anxiety satisfies this criteria.

Specifically, the American Psychiatric Association defines anxiety and anxiety disorders as conditions characterized by excessive fear and behavioral disturbances. Anxiety results from anticipation of a future threat and may be associated with symptoms of muscle tension, vigilance in preparation for future danger, and overly cautious or avoidant behaviors. Additionally, there are multiple ICD-10-CM codes for anxiety disorders. Because anxiety maintains a common definition in the medical community and has ICD-10-CM codes, I find that anxiety is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are

generally accepted by the medical community and other experts as valid treatments for the condition. From my review of this condition, the generally accepted treatments for anxiety are dependent on the symptoms and the severity of the particular disorder.

Mild and moderate forms of anxiety may not require a pharmacologic intervention, but may necessitate other forms of treatment, such as meditation, mindfulness, breathing techniques as well as psychotherapy (counseling) or cognitive therapy.⁴⁸ The most common classes of medications used to combat anxiety disorders are antidepressants, anti-anxiety drugs, and beta-blockers.⁴⁹ Antidepressants are safe and effective but they may be risky for children, teens, and young adults.⁵⁰ Antidepressants also come with a "black box" warning — the FDA's strongest warning — advising that some people may have suicidal thoughts or make suicide attempts while taking the medication.⁵¹ The most common anti-anxiety medications are called benzodiazepines.

As noted by the Panel, the common side effects of benzodiazepines include headache, confusion, tiredness, and in some cases nightmares and memory impairments.⁵² And, benzodiazepines carry a risk of dependence and addiction.⁵³ Furthermore, the FDA notes that the number of patients who were prescribed both an opioid analgesic and benzodiazepine increased by 41% between 2002 and 2014.⁵⁴ As a result, the FDA requires black box warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines to inform the patient about the serious risks associated with using these medications at the same time.⁵⁵ Thus, I find that the treatments for anxiety are recognized and accepted by the medical community as the treatments for this condition and relate to the suffering of the patient.

As for the third factor, which is whether the condition itself and for the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the anxiety condition itself as well as the treatments for this condition cause severe suffering for patients. Specifically, anxiety may lead to problems that negatively impact an individual's activities of daily living and quality of life and may lead to suicide and depression. Anxiety disorders can also cause significant distress or interfere with social, occupational, and other areas of functioning. In fact, an estimated 31.1% of U.S. adults experience an anxiety disorder at some time in their lives.⁵⁶ Medications, in some instances, may exacerbate the symptoms and are associated with debilitating side effects that can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that both the condition of anxiety as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and or the treatment thereof. As discussed above, mild and moderate forms of anxiety may be treated with meditation, mindfulness, breathing techniques as well as counseling or cognitive therapy that can be effective. Progression to medication therapy may be initiated; however, in both instances, one must consider the therapeutic response. Failure to respond to therapies or side effects associated with treatments may result in significant impacts on quality of life. As such, I find that there is an absence of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for migraine that cause suffering.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that cannabis is generally accepted as an effective treatment for anxiety.

The Panel discussed medical evidence that cannabis may exacerbate anxiety symptoms or that an effect related to cannabis may be associated with anxiety, such as dependence and cravings. Literature suggests that individuals with anxiety sensitivity may be more likely to turn to cannabis as a mechanism for coping with stress, which may in turn lead to problematic use behaviors.⁵⁷ However, the Panel further discussed a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, which found that there is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, which was assessed by a public speaking test utilizing individuals with social anxiety disorders.⁵⁸

On balance, the Panel recommended adding anxiety as an allowable condition under the MMP as research suggests that it could be helpful to some patients with this condition. I agree. While marijuana may not be effective for all anxiety sufferers, there is research evidencing that it may be helpful to some, especially those with social anxiety disorders. Thus, I find that there is acceptance in the medical community that marijuana is

likely to relieve the suffering associated with some anxiety conditions. However, like any medical condition, the use of medical marijuana to treat anxiety must be explored by the medical professional treating the patient to determine whether it is the best and most appropriate course of treatment for the patient.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of anxiety under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of anxiety is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that anxiety should be added to the MMP.

In a previous qualifying condition petition for Generalized Anxiety Disorder, the Director of Health at the Hawaii Department of Health rejected adding the condition to the medical marijuana program. The main reason being that there is a lack of peer-reviewed scientific evidence showing beneficial use to treat GAD. This idea that peer-reviewed scientific evidence needs to conclusively show medical benefit or else no other qualifying conditions could be approved is wrong; due to the political nature of marijuana. Please allow me to explain.

The Hawaii medical cannabis law was created based on medical and anecdotal evidence. Anecdotal evidence was accepted because there is a lack of scientific research on the benefits of marijuana. Due to cannabis’s placement in schedule 1 of controlled substances in both state and federal laws. Quoting from the Hawaii Medical Cannabis Law:

https://www.capitol.hawaii.gov/session2000/acts/Act228_SB862_HD1_.htm

There is sufficient medical and **anecdotal evidence** to support the proposition that these diseases and conditions may respond favorably to a medically controlled use of marijuana.

This lack of research is due to the funding of marijuana research being regulated by NIDA, the National Institute of Drug Abuse. NIDA’s purpose is investigating the abuse potential of drugs, including cannabis, with focus solely on trying to prove the negatives of marijuana use. Since NIDA funds negative effects of marijuana research, research is granted on the flimsiest of theories and has corrupted and biased science. Forcing researchers to chase more NIDA grants for research to ensure they continue to have jobs.

Negative research findings are promoted wildly by NIDA when they are published. Even if the methodology of the study is flawed beyond belief. Even when other researchers try to duplicate the results and fail, NIDA continues to promote the flawed study as though it still has merit. An example of this can be found on NIDA's website

<https://www.drugabuse.gov/news-events/nida-notes/2016/08/study-questions-role-marijuana-in-teen-users-iq-decline>

This finding suggests that the twins’ IQ was affected by factors that twins share in their genes or family background, rather than factors in which they differed (e.g., drug use). A further analysis, comparing the impact of marijuana use on fraternal versus identical twins, suggested that family-wide environmental influences are more decisive than genes for determining IQ trajectory.

NIDA, without any evidence to back up the statement, goes on:

These findings contrast but are not entirely inconsistent with those of an earlier study that linked teen-onset regular marijuana use to IQ deficits in the fourth decade of life (see Early-Onset, Regular Cannabis Use Is Linked to IQ Decline). The researchers say that although their evidence indicates that marijuana exposure does not cause persistent loss of intellectual function up to age 20, **prolonged regular exposure for decades might do so.**

NIDA contradicts itself often, and continues to promote failed theories that bear no relationship to reality. Especially trying to say that marijuana is a gateway drug.

<https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-gateway-drug>

These findings are consistent with the idea of marijuana as a "gateway drug." However, the majority of people who use marijuana do not go on to use other, "harder" substances.

A more sinister theory promoted by NIDA, the DEA, and even physicians is that marijuana use increases the risk of Schizophrenia. This is so unbelievable that it is a slap in the face of science. Simply looking at reality, the larger numbers of people using, or admitting to use of marijuana, the large number of registered medical cannabis patients in the USA (roughly 1,000,000 to 2,000,000) and the flat schizophrenia rates as reported by the NIH and WHO completely invalidate all peer-reviewed published research on the topic of marijuana causing schizophrenia.

<https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml>

<https://www.who.int/news-room/fact-sheets/detail/schizophrenia>

In fact, a percentage of people diagnosed with schizophrenia use marijuana to reduce anxiety and help with symptoms. People with more severe schizophrenia use more marijuana, this is the basis for the theory that marijuana causes more severe symptoms of schizophrenia. Similar thinking is used against patients who have more severe pain, that marijuana somehow makes pain worse for patients and they have to use more marijuana to gain pain relief. Instead of the observable theory that people with more severe pain use more marijuana to treat their more severe pain than people who have less severe pain. No one makes the theory that aspirin makes pain worse, because people with more pain use more aspirin. Bad science.

The whole point of a state medical marijuana law is that the federal government has engineered a catch-22 circular logic loop about marijuana. States, mostly via people's ballot initiatives have sideswiped the FDA in approving a medicine. This is because the FDA has adopted a policy of only endorsing and approving of monotherapies, e.g. one or two isolated and specific chemicals per approved medicine. There is another policy to reject crude botanical medicines due to variations from plant to plant. These comments by the FDA are found in the DEA response to a petition to reschedule marijuana to schedule 2 and in congressional testimony. Even if a company submitted an IND to the FDA to study marijuana for the treatment of a disease, it would be rejected by the FDA on both of those policies.

The catch-22 comes when patients, nurses, physicians, governors, senators and representatives suggest that marijuana be investigated as a medicine. In congressional testimony, the FDA says we need more research before endorsing that. NIDA says we need more research before utilizing marijuana as a medicine. The DEA says we need more research before marijuana could be considered a medicine. So, if everyone agrees we need more research, where exactly is the research?

Individual physicians have attempted to research the benefits of marijuana within universities. What happens is that, at every turn, approval to study is blocked, delayed and rejected. See for example the 10 years of trying to study medical marijuana for treatment of PTSD in veterans.

<https://www.stripes.com/marijuana-ptsd-study-concludes-after-10-years-of-planning-research-1.570986>

Sisley and her team had to gain approval and support from the U.S. Food and Drug Administration, the Drug Enforcement Administration and the National Institute on Drug Abuse to initiate the research – a process that lasted years.

One study took several years just to begin. After NIDA provided marijuana for research that was full of seeds, stems and mold.

<https://health.hawaii.gov/medicalcannabisregistry/files/2017/08/Generalized-Anxiety-Disorder-08.09.17-Redacted.pdf>

The GAD petition submitted in 2017 included anecdotal evidence, peer-reviewed patient surveys, marijuana use reports and other information. It was rejected by the director due to not having enough peer-reviewed scientific research. One reason given for the rejection was that there was "no specific evidence to GAD". This is why exact specific conditions and waiting for peer-reviewed medical research will never work as an administrative rule for reviewing qualifying condition petitions. There will never be medical marijuana research that specifically mentions each of the hundreds of conditions that include anxiety as a symptom. Research studies are done with one drug and one condition. A rejection for not having a specific condition mentioned seems more like a pedantic nitpick and less like a legitimate reason when both GAD and anxiety share anxiety as the core symptom.

This GAD petition rejection uses the same reason the federal government does not approve of medical marijuana. If this requirement barrier of peer-reviewed research was erected, no state would have a medical marijuana program. Due to the federal policies which are a de facto prohibition on research for medical marijuana benefits. These state medical marijuana programs were created because the federal government failed to do research, and continues to prohibit new research. While the reality is that cannabis is a non toxic medicine, has always been a medicine and always will be a

medicine.

Anxiety was also included with a bill in the Hawaii legislature to add qualifying conditions. The Department of Health testified, and in opposing the bill, the DOH stated it would rather include conditions via the petition process. The HDOH also gave another reason, that the dept wanted to delay adding the condition until dispensaries were active. Try naming another medication that is delayed and kept illegal because the department was waiting for a pharmacy to open. The DOH needs to stop these petty games played with sick people's lives.

(REF #95) https://www.capitol.hawaii.gov/session2018/testimony/SB174_TESTIMONY_CPH_02-08-17.pdf

This is another wrong-headed approach to the process, and ignores why and what the medical marijuana law does. Allow me to explain the purpose of the law and the role of the DOH in it.

From the Hawaii medical cannabis law:

The legislature is aware of the legal problems associated with the legal acquisition of marijuana for medical use. However, the legislature believes that medical scientific evidence on the medicinal benefits of marijuana should be recognized.

...

Therefore, the purpose of this Act is to ensure that seriously ill people are not penalized by the State for the use of marijuana for strictly medical purposes when the patient's treating physician provides a professional opinion that the benefits of medical use of marijuana would likely outweigh the health risks for the qualifying patient.

The whole point of the medical marijuana program is not to endorse, nor recommend medical marijuana to patients. The purpose of the law is to NOT PENALIZE patients using medical marijuana with recommendations from their physicians. To protect patients from the laws prohibiting the use of marijuana.

Said another way, it is not the Department of Health's role to become the FDA and research medical marijuana. It is not the DOH's role to judge if medical marijuana is a medicine or not. It is not the DOH's role to decide which conditions marijuana is beneficial for either. That role is solely for a patient to decide if medical marijuana works for their conditions or not. Physicians have a role to make sure the patient's health is first priority over any medication.

The DOH's only role in the petition process is to protect medical marijuana patients from arrest.

People are currently illegally using marijuana to treat their conditions, specifically anxiety. The DOH has the power to protect these patients by adding qualifying conditions. Instead, the DOH has assumed the role of the FDA, denying petitions and opposing adding conditions legislatively. Waiting for peer-reviewed medical evidence that by all accounts is not coming within the next two decades.

This delay and denial of the reality of medical marijuana patients conditions needs to stop.

- (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.

Anxiety is accepted by the medical community as a valid existing medical condition affecting millions of Americans each year. The CDC, NIH and Veterans Affairs all have in-depth websites dedicated to anxiety and treatment.

<https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml>

The wide variety of anxiety disorders differ by the objects or situations that induce them, but share features of excessive anxiety and related behavioral disturbances. Anxiety disorders can interfere with daily activities such as job performance, school work, and relationships.

Based on diagnostic interview data from the National Comorbidity Study Replication (NCS-R), Figure 1 shows past year prevalence of any anxiety disorder among U.S. adults aged 18 or older.¹

An estimated 19.1% of U.S. adults had any anxiety disorder in the past year.

Past year prevalence of any anxiety disorder was higher for females (23.4%) than for males (14.3%).

An estimated 31.1% of U.S. adults experience any anxiety disorder at some time in their lives.

Anxiety affects a large portion of the people in the United States, costing billions of dollars in medical treatment costs.

<https://www.cdc.gov/mentalhealth/basics/burden.htm>

Anxiety:

- Anxiety disorders, which include panic disorder, generalized anxiety disorder, post-traumatic stress disorder, phobias, and separation anxiety disorder, are the most common class of mental disorders present in the general population.
- The estimated lifetime prevalence of any anxiety disorder is over 15%, while the 12-month prevalence is more than 10%.
- Prevalence estimates of anxiety disorders are generally higher in developed countries than in developing countries.
- Most anxiety disorders are more prevalent in women than in men.
- One study estimated the annual cost of anxiety disorders in the United States to be approximately \$42.3 billion in the 1990s, a majority of which was due to non-psychiatric medical treatment costs. This estimate focused on short-term effects and did not include the effect of outcomes such as the increased risk of other disorders.

Veterans suffer from Anxiety and related disorders.

<https://pubmed.ncbi.nlm.nih.gov/15127904/>

Results: Veterans of the first Gulf War reported a markedly higher prevalence of current anxiety disorders than nondeployed military personnel (5.9% vs. 2.8%; odds ratio = 2.1; 95% confidence interval = 1.3-3.1), and their anxiety disorders are associated with co-occurring psychiatric disorders. Posttraumatic stress disorder, panic disorder, and generalized anxiety disorder were each present at rates nearly twice expected. In our multivariate model, predeployment psychiatric treatment and predeployment diagnoses (posttraumatic stress disorder, depression, or anxiety) were independently associated with current anxiety disorder. Participation in Gulf War combat was independently associated with current posttraumatic stress disorder, panic disorder, and generalized anxiety disorder.

(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.

Anxiety can cause a person to withdrawal from talking to other people or even going outside. Anxiety can diminish or completely debilitate a person from interviewing for a job, making day to day decisions, making personal relationships or thriving.

Instead of dealing and treating anxiety, the world instead decided to call anxiety being an introvert. An "introvert" is a "shy, reticent person". In other words, a person who has so much anxiety that they would rather hide than speak to someone else. Shyness is anxiety.

<https://www.nimh.nih.gov/health/publications/social-anxiety-disorder-more-than-just-shyness/index.shtml>

The reason this petition is for "Anxiety" and not "social anxiety disorder" is because each year there seems to be a newly named disorder with the core symptom being anxiety. Panic Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, Seasonal Affective disorder, PTSD. Anxiety is the common condition.

<https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml>

Any Anxiety Disorder with Impairment Among Adults

Of adults with any anxiety disorder in the past year, degree of impairment ranged from mild to severe, as shown in Figure 2. Impairment was determined by scores on the Sheehan Disability Scale.

Among adults with any anxiety disorder, an estimated 22.8% had serious impairment, and 33.7% had moderate impairment.¹

A majority of people with any anxiety disorder experienced mild impairment (43.5%).¹

1. Harvard Medical School, 2007. National Comorbidity Survey (NCS). (2017, August 21). Retrieved from <https://www.hcp.med.harvard.edu/ncs/index.php>. Data Table 2: 12-month prevalence DSM-IV/WMH-CIDI disorders by sex and cohort.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC181171/>

Although the principal symptoms of anxiety disorders include fear, excessive worry, nervousness, and obsessions, a multitude of physical symptoms also may be present. These somatic symptoms—which include heart palpitations, gastrointestinal problems, sweating, fainting, and chronic pain—can confound the diagnosis and resist all forms of medical management, unless the underlying anxiety source is identified and treated. Delays in diagnosis and treatment can be expensive for the patient, physician, and society: unnecessary tests and ineffective treatments increase medical costs, and **anxiety symptoms may lead to loss of income and productivity, financial dependence, and even suicide.**

<https://www.healthline.com/nutrition/anxiety-disorder-symptoms>

11 Signs and Symptoms of Anxiety Disorders

Many people experience anxiety at some point in their lives.

In fact, anxiety is a very normal response to stressful life events like moving, changing jobs or having financial troubles.

However, when symptoms of anxiety become larger than the events that triggered them and begin to interfere with your life, they could be signs of an anxiety disorder.

Anxiety disorders can be debilitating, but they can be managed with proper help from a medical professional. Recognizing the symptoms is the first step.

Here are 11 common symptoms of an anxiety disorder, as well as how to reduce anxiety naturally and when to seek professional help.

1. Excessive Worrying

One of the most common symptoms of an anxiety disorder is excessive worrying.

The worrying associated with anxiety disorders is disproportionate to the events that trigger it and typically occurs in response to normal, everyday situations ([1Trusted Source](#)).

To be considered a sign of generalized anxiety disorder, the worrying must occur on most days for at least six months and be difficult to control ([2Trusted Source](#)).

The worrying must also be severe and intrusive, making it difficult to concentrate and accomplish daily tasks.

People under the age of 65 are at the highest risk of generalized anxiety disorder, especially those who are single, have a lower socioeconomic status and have many life stressors ([3Trusted Source](#)).

2. Feeling Agitated

When someone is feeling anxious, part of their sympathetic nervous system goes into overdrive.

This kicks off a cascade of effects throughout the body, such as a racing pulse, sweaty palms, shaky hands and dry mouth (4).

These symptoms occur because your brain believes you have sensed danger, and it is preparing your body to react to the threat.

Your body shunts blood away from your digestive system and toward your muscles in case you need to run or fight. It also increases your heart rate and heightens your senses (5Trusted Source).

While these effects would be helpful in the case of a true threat, they can be debilitating if the fear is all in your head.

Some research even suggests that people with anxiety disorders are not able to reduce their arousal as quickly as people without anxiety disorders, which means they may feel the effects of anxiety for a longer period of time (6Trusted Source, 7Trusted Source).

3. Restlessness

Restlessness is another common symptom of anxiety, especially in children and teens.

When someone is experiencing restlessness, they often describe it as feeling “on edge” or having an “uncomfortable urge to move.”

One study in 128 children diagnosed with anxiety disorders found that 74% reported restlessness as one of their main anxiety symptoms (8Trusted Source).

While restlessness does not occur in all people with anxiety, it is one of the red flags doctors frequently look for when making a diagnosis.

If you experience restlessness on the majority of days for more than six months, it may be a sign of an anxiety disorder (9Trusted Source).

4. Fatigue

Becoming easily fatigued is another potential symptom of generalized anxiety disorder.

This symptom can be surprising to some, as anxiety is commonly associated with hyperactivity or arousal.

For some, fatigue can follow an anxiety attack, while for others, the fatigue can be chronic.

It's unclear whether this fatigue is due to other common symptoms of anxiety, such as insomnia or muscle tension, or whether it may be related to the hormonal effects of chronic anxiety (10Trusted Source).

However, it is important to note that fatigue can also be a sign of depression or other medical conditions, so fatigue alone is not enough to diagnose an anxiety disorder (11Trusted Source).

5. Difficulty Concentrating

Many people with anxiety report having difficulty concentrating.

One study including 157 children and teens with generalized anxiety disorder found that more than two-thirds had difficulty concentrating (12Trusted Source).

Another study in 175 adults with the same disorder found that almost 90% reported having difficulty concentrating. The worse their anxiety was, the more trouble they had (13Trusted Source).

Some studies show that anxiety can interrupt working memory, a type of memory responsible for holding short-term information. This may help explain the dramatic decrease in performance people often experience during periods of high anxiety ([14Trusted Source](#), [15Trusted Source](#)).

However, difficulty concentrating can also be a symptom of other medical conditions, such as an attention deficit disorder or depression, so it is not enough evidence to diagnose an anxiety disorder.

6. Irritability

Most people with anxiety disorders also experience excessive irritability.

According to one recent study including over 6,000 adults, more than 90% of those with generalized anxiety disorder reported feeling highly irritable during periods when their anxiety disorder was at its worst ([16Trusted Source](#)).

Compared to self-reported worriers, young and middle-aged adults with generalized anxiety disorder reported more than twice as much irritability in their day-to-day lives ([17Trusted Source](#)).

Given that anxiety is associated with high arousal and excessive worrying, it is not surprising that irritability is a common symptom.

7. Tense Muscles

Having tense muscles on most days of the week is another frequent symptom of anxiety.

While tense muscles may be common, it's not fully understood why they're associated with anxiety.

It is possible that muscle tenseness itself increases feelings of anxiety, but it is also possible that anxiety leads to increased muscle tenseness, or that a third factor causes both.

Interestingly, treating muscle tension with muscle relaxation therapy has been shown to reduce worry in people with generalized anxiety disorder. Some studies even show it to be as effective as cognitive behavioral therapy ([18Trusted Source](#), [19Trusted Source](#)).

8. Trouble Falling or Staying Asleep

Sleep disturbances are strongly associated with anxiety disorders ([20Trusted Source](#), [21Trusted Source](#), [22Trusted Source](#), [23Trusted Source](#)).

Waking up in the middle of the night and having trouble falling asleep are the two most commonly reported problems ([24Trusted Source](#)).

Some research suggests that having insomnia during childhood may even be linked to developing anxiety later in life ([25Trusted Source](#)).

A study following nearly 1,000 children over 20 years found that having insomnia in childhood was linked to a 60% increased risk of developing an anxiety disorder by age 26 ([26Trusted Source](#)).

While insomnia and anxiety are strongly linked, it is unclear whether insomnia contributes to anxiety, if anxiety contributes to insomnia, or both ([27Trusted Source](#), [28Trusted Source](#)).

What is known is that when the underlying anxiety disorder is treated, insomnia often improves as well ([29Trusted Source](#)).

9. Panic Attacks

One type of anxiety disorder called panic disorder is associated with recurring panic attacks.

Panic attacks produce an intense, overwhelming sensation of fear that can be debilitating.

This extreme fear is typically accompanied by rapid heartbeat, sweating, shaking, shortness of breath, chest tightness, nausea and fear of dying or losing control ([30Trusted Source](#)).

Panic attacks can happen in isolation, but if they occur frequently and unexpectedly, they may be a sign of panic disorder.

An estimated 22% of American adults will experience a panic attack at some point in their lives, but only about 3% experience them frequently enough to meet the criteria for panic disorder ([31Trusted Source](#)).

10. Avoiding Social Situations

You may be exhibiting signs of social anxiety disorder if you find yourself:

- Feeling anxious or fearful about upcoming social situations
- Worried that you may be judged or scrutinized by others
- Fearful of being embarrassed or humiliated in front of others
- Avoiding certain social events because of these fears

Social anxiety disorder is very common, affecting roughly 12% of American adults at some point in their lives ([32Trusted Source](#)).

Social anxiety tends to develop early in life. In fact, about 50% of those who have it are diagnosed by age 11, while 80% are diagnosed by age 20 ([33Trusted Source](#)).

People with social anxiety may appear extremely shy and quiet in groups or when meeting new people. While they may not appear distressed on the outside, inside they feel extreme fear and anxiety.

This aloofness can sometimes make people with social anxiety appear snobby or standoffish, but the disorder is associated with low self-esteem, high self-criticism and depression ([34Trusted Source](#)).

11. Irrational Fears

Extreme fears about specific things, such as spiders, enclosed spaces or heights, could be a sign of a phobia.

A phobia is defined as extreme anxiety or fear about a specific object or situation. The feeling is severe enough that it interferes with your ability to function normally.

Some common phobias include:

- **Animal phobias:** Fear of specific animals or insects
- **Natural environment phobias:** Fear of natural events like hurricanes or floods
- **Blood-injection-injury phobias:** Fear of blood, injections, needles or injuries
- **Situational phobias:** Fear of certain situations like an airplane or elevator ride

Agoraphobia is another phobia that involves fear of at least two of the following:

- Using public transportation
- Being in open spaces
- Being in enclosed spaces
- Standing in line or being in a crowd
- Being outside of the home alone

Phobias affect 12.5% of Americans at some point in their lives. They tend to develop in childhood or the teenage years and are more common in women than men ([35Trusted Source](#), [36Trusted Source](#)).

(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 anxiety. Not the treatment of anxiety. Anti-anxiety medications are a valid treatment generally accepted by the medical community and can cause serious side effects and death.

https://www.medicinenet.com/sertraline_zoloft_vs_venlafaxine_effexor/article.htm

What are the side effects of sertraline and venlafaxine?

Sertraline

The most common side effects of sertraline are:

- Sleepiness
- Nervousness
- Insomnia
- Dizziness
- Nausea
- Tremor
- Skin rash
- Constipation
- Upset stomach
- Loss of appetite
- Headache
- Diarrhea
- Abnormal ejaculation
- Decreased interest in sexual activity
- Dry mouth
- Increase in sweating, known as diaphoresis
- Weight loss

Possible serious side effects of sertraline include:

- Irregular heartbeats
- Serious allergic reactions
- Worsening of depression
- Serotonin syndrome
- Hyponatremia
- Abnormal bleeding
- Priapism (prolonged erection)
- Decreased liver function
- Suicidality
- Activation of mania in patients with bipolar disorder

Important side effects are irregular heartbeats, allergic reactions and activation of mania in patients with bipolar disorder.

If sertraline is discontinued abruptly, some patients experience side effects such as:

- Abdominal cramps
- Fatigue
- Nausea
- Vomiting
- Diarrhea
- Headaches
- Lightheadedness

- Dizziness
- Diminished appetite
- Flu-like symptoms
- Sweating
- Chills
- Sleep disturbances
- Memory impairment

A gradual dose reduction of sertraline is recommended when therapy is discontinued.

Venlafaxine

WARNING

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with depression and other psychiatric disorders. Anyone considering the use of venlafaxine or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be closely observed for clinical worsening, suicidality, or unusual changes in behavior.

Venlafaxine, like most antidepressants, can cause:

- Nausea
- Headaches
- Anxiety
- Insomnia
- Drowsiness
- Loss of appetite

Other side effects that can occur are:

- Dizziness
- Ejaculation disorder
- Sweating
- Dry mouth
- Weight loss

Increased blood pressure can occur, and blood pressure should be monitored.

Seizures have been reported.

(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.

(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.

Selected quotes and transcribed tables are taken from the following research and presented below.

1. <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.

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%).

3. <https://doi.org/10.1016/j.jpain.2007.09.002>

A randomized, double-blind, placebo-controlled trial was conducted to determine the benefit of nabilone in pain management and quality of life improvement in 40 patients with fibromyalgia.

There were significant decreases in the VAS, FIQ, and anxiety in the nabilone treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks, respectively. Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with significant benefits in pain relief and functional improvement.

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

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.

5. <https://doi.org/10.1080/02791072.2011.587700>

Of 1,746 patients, 37.8% self-reported therapeutic benefits from medical marijuana for anxiety.

16.9% of patients self-reported therapeutic benefits from medical marijuana for panic attacks.

6. <https://www.ncbi.nlm.nih.gov/pubmed/6117575>

The results of the study showed a dramatic improvement in anxiety in the nabilone group when compared with placebo (P less than 0.001). Side effects reported were dry mouth, dry eyes, and drowsiness. Patients did not report any of the subjective "altered state" experience of marijuana.

7. <https://www.ncbi.nlm.nih.gov/pubmed/15857739>

Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), **anxiety (93%)**, nerve pain (90%), depression (86%), and paresthesia (85%).

8. <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.

9. <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.

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

Of 21 patients reporting stress, 20 said medical marijuana helped moderate-complete relief.

Of 16 patients reporting mood, all 16 said medical marijuana helped moderate-complete relief.

The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood,

stiffness/spasm, and pain.

11. <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.

12. <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.

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

367 medical marijuana patients in Arizona were surveyed.

181 patients reported using medical marijuana to experience relief from Anxiety

164 patients reported using medical marijuana to experience relief from Stress.

General relief from Anxiety symptoms was 82.9% and 87.2% for Stress,

Relief by medical marijuana compared to other medications was 79.3% for Anxiety and 91.6 for Stress.

Less frequent use of other medications was 85.9% for Anxiety and 79.1% for Stress.

14. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3285527/>

One Hundred Canadian medical marijuana patients were surveyed in 2007-2008. 60.2% said they used medical marijuana to reduce anxiety.

15. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1262744/>

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.

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.

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%).

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 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. 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%).

16. <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.

17. <https://doi.org/10.1111/dar.12323>

Participants presented with the range of conditions that is generally consistent with surveys of CTP users, the most prominent conditions being pain (32%), mood (i.e. anxiety and depression (18%), arthritis (15%), HIV (10%), gastrointestinal disorder (7%)

18. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5422566/>

We previously reported in an earlier survey that of 1,429 respondents, 61% reported using cannabis for managing pain, 58% reported using cannabis for anxiety and 50% reported using cannabis for depression. In the current analysis, these same conditions were also the most commonly reported conditions by respondents. Of the 1,040 participants reporting pain and/or intractable pain, 619 (59.52%) reported depression and anxiety as comorbidities. As such, the odds of reporting substituting cannabis for prescription drugs were more than one and a half times greater (OR, 1.66; 95% CI, 1.27–2.16) among those reporting using it to manage pain, anxiety and depression than among those using it to manage only one of the three conditions.

This team previously reported that in a survey of 1,429 medical cannabis users, 61% reported cannabis use for pain, 58% reported cannabis use for anxiety and 50% reported using cannabis to manage depression. In 2016, Dale and Stacey reported that those using cannabis for pain were more likely to be substituting for prescription drugs. In 2017, Walsh et al published a review of medical cannabis and mental health to try to better understand how medical cannabis use may impact areas of potential concern for clinicians. “Relaxation and relief of anxiety” and “relief of negative mood” or depression were among the most widely reported conditions in 60 publications included in their analysis. Because it is common for chronic pain patients to be prescribed combinatorial pharmacotherapy to address comorbidity with depression and/or anxiety, it is largely unknown how often patients may be discontinuing prescription medications when initiating cannabis use.

Taken with preclinical data on the role of the endocannabinoid system in stress, pain processing and immune homeostasis, it is clear that future investigation is warranted using controlled trials with human subjects to better understand the role that cannabis may play in treating pain, anxiety, depression and other conditions.

19. <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.

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

Of 628 Canadian medical marijuana patients:

463 patients reported using medical marijuana to treat anxiety.

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.

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.

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.

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

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]

22. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3691841/>

While the controversies surrounding cannabis are far from subdued (and are often permeated and masked by conflicting ideological credos), standardized studies on cannabinoids have highlighted that the psychological and behavioral outcomes of this substance are highly variable and range from relaxation, euthymia and heightened sociability to panic, paranoid ideation and psychosis [112 - 116]. A corollary of this observation is that the high comorbidity rate between cannabis use disorders and psychiatric conditions [100 - 105] may indicate that cannabis consumption is either a concurring cause or a "self-therapeutic" strategy for anxiety and mood disorders [117 - 123]. The latter interpretation is supported by the observation that anxiety-spectrum disturbances and traumas in early developmental stages are a strong predictor for later cannabis use disorders [124 - 127]; furthermore, several lines of evidence suggest that the anxiolytic effects of THC may partially account for the high prevalence of cannabis use in patients affected by PTSD [128 - 131] and OCD [132]. Accordingly, recent clinical studies have shown that THC elicits therapeutic effects in OCD [133] and trichotillomania, an impulse-control disorder characterized by compulsive hair-pulling [134].

23. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604171/>

Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

24. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604174/>

Although clinical studies in this area are difficult to do, even in countries where the use of cannabis has been allowed for years, there is a clear role for cannabis products in symptom management for these difficult conditions.

25. <https://www.ncbi.nlm.nih.gov/pubmed/22729452>

RESULTS:

Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder.

CONCLUSION:

Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

26. <https://doi.org/10.2202/1941-2851.1017>

1655 Patients reported using medical marijuana for these conditions:
Anxiety disorders 18.7% of patients

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.

27. <https://doi.org/10.1176/appi.ajp.2007.07061016>

Hence, it can be speculated that the anti-obsessive effect observed in our patients may have been a consequence of the glutamate modulation of the cannabinoid dronabinol.

28. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4349825/>

The findings from the study indicate that cannabis use is associated with a subsequent change in positive affect, depressive symptoms and manic symptoms over the course of daily life. No evidence for the use of cannabis to self-medicate minor fluctuations in negative affect or BD symptoms was revealed. Participants in the study were currently well and out of episode. Future research should explore whether the self-medication hypothesis is more relevant to individuals that are in the acute stages of depression or mania. This would be consistent with the broader self-medication hypothesis in BD where individuals have reported finding cannabis useful in the management of their symptoms.

29. <https://www.ncbi.nlm.nih.gov/pubmed/9692379>

The authors present case histories indicating that a number of patients find cannabis (marijuana) useful in the treatment of their bipolar disorder. Some used it to treat mania, depression, or both. They stated that it was more effective than conventional drugs, or helped relieve the side effects of those drugs. One woman found that cannabis curbed her manic rages; she and her husband have worked to make it legally available as a medicine.

Others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects. Another case illustrates the fact that medical cannabis users are in danger of arrest, especially when children are encouraged to inform on parents by some drug prevention programs. An analogy is drawn between the status of cannabis today and that of lithium in the early 1950s, when its effect on mania had been discovered but there were no controlled studies. In the case of cannabis, the law has made such studies almost impossible, and the only available evidence is anecdotal. The potential for cannabis as a treatment for bipolar disorder unfortunately can not be fully explored in the present social circumstances.

30. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4898690/>

Findings suggest that for some bipolar patients, marijuana may result in partial alleviation of clinical symptoms. Moreover, this improvement is not at the expense of additional cognitive impairment.

31. <https://www.ncbi.nlm.nih.gov/pubmed/17703715>

Subjective reports by patients suggest an overall positive effect, but these may be unreliable. We herein report a case in which mood data was prospectively collected over two years of total substance abstinence and two years of extreme marijuana use. Marijuana use did not alter the total number of days of abnormal mood, however, marijuana was associated with an increase in the number of hypomanic days and a decrease in the number of depressed days. While not conclusive, the data suggest that marijuana may indeed have an effect on mood in bipolar patients that needs to be systematically examined.

32. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652027/>

Cannabis use diminishes some of the adverse effects of neurological and psychiatric disorders.

33. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4323143/>

These results suggest that cannabis use has clinical implications for the early course of BD (Bipolar Disorder) by increasing mood level.

34. <https://doi.org/10.1111/j.1368-5031.2005.00271.x>

Medicinal cannabis use was Reported by patients with chronic pain(25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (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 in the United States. 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 anxiety.

In its first year of reports, the Minnesota DOH published patient comments about the beneficial effects of the medical marijuana.

(REF #98) <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>

Many such comments are found within the above report.

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

<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 anxiety symptoms, and a large percentage of patients continue to maintain that reduction of anxiety for 4 months.

(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 which show a very small percentage of people experience a worsening of anxiety symptoms. I urge you to read them all as it shows how small the number of adverse anxiety 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

Although the comments mention anxiety as a side effect, sometimes it is not the cannabis's fault, but prohibition's fault, as this comment rated at score level 4 shows:

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!

Massachusetts published a report on its medical marijuana patients and their benefits.

<https://www.mass.gov/report/massachusetts-department-of-public-health-marijuana-research>
(REF #77) <https://www.mass.gov/files/documents/2019/07/09/MBHS-full-report-final.pdf>

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 mood and or mental health for a large percentage of people.

Page 10:

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.

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.**

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

See Attached

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.

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,



Margaret Maupin, APRN

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.



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.

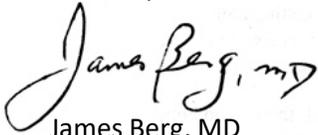
There are many conditions that cannabis is helpful for, but there are three conditions that cannabis is especially helpful for, yet even after twenty years of the program, depression, anxiety and insomnia remain off the qualification list. Cannabis has been labeled in the past as an "euphoric agent" 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



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

**VII. The Potential of Cannabinoid
Derived Therapy in Anxiety,
Spasticity, and Epilepsy**

The Efficacy and Safety of Nabilone (A Synthetic Cannabinoid) in the Treatment of Anxiety

LOUIS F. FABRE, M.D., Ph.D., and DAVID McLENDON, Ph.D. Houston, Tex.

Abstract: The anxiolytic properties of nabilone, a synthetic cannabinoid resembling the natural cannabinoids, were studied in 25 outpatients suffering from anxiety. The drug was compared with a placebo in a double-blind manner over a 28-day treatment period. Patients were seen weekly by the physician and were rated by the Hamilton Rating Scale for Anxiety and the Patient's Global Evaluation as well as by patient-rated evaluations. The results of the study showed a dramatic improvement in anxiety in the nabilone group when compared with placebo ($P < 0.001$). Side effects reported were dry mouth, dry eyes, and drowsiness. Patients did not report any of the subjective "altered state" experience of marihuana.

THE marihuana plant has been used by man for various ailments and for pleasure for thousands of years. As recently as 40 years ago, cannabis was a recognized drug in the *United States Pharmacopeia*. It then fell into therapeutic disuse. Recent research has indicated that cannabis (Δ^9 -tetrahydrocannabinol, THC) and cannabinoid-like compounds may represent a class of compounds that are of potential therapeutic value.¹⁻³ Marihuana is now considered to be useful in the treatment of glaucoma and the nausea associated with cancer chemotherapy.



Nabilone* is a synthetic cannabinoid which resembles the cannabinoids but is not a tetrahydrocannabinol. Preclinical research indicates that nabilone has anal-

gesic, antianxiety, and antipsychotic properties and is a drug with a wide margin of safety.⁴

More recent research found nabilone to be active in single doses of 1 to 5 mg, with 1- and 2.5-mg doses inducing relaxant and sedative effects in all of six subjects. Euphoria, dry mouth, tachycardia, or postural hypotension were not seen in 1-mg doses although slight effects were noted at 2.5 mg and marked effects at 5 mg. Tolerance developed to the side effects of the drug after two days.⁵ No significant tachycardia developed at any dose. This research indicated that nabilone may have utility in the treatment of psychoneurotic anxiety.

Our research group set out to systematically study the anxiolytic effects of nabilone. Three studies were planned: first, a dose-rising open-label study to assess the proper dose range of nabilone; second, a double-blind study against placebo to assess the efficacy of nabilone.⁶ Finally, the third study was a double-blind study of nabilone against placebo and diazepam to assess the relative efficacy of nabilone to a standard anxiolytic. The first and second studies were performed and are discussed.

From Research Testing, Inc., and the Fabre Clinic, Houston, Tex. 77004.

* Eli Lilly and Company.

The third study was begun but canceled before any data could be gathered. The sponsor had experienced side effects in their ongoing cancer antiemetic studies which they felt made nabilone not a proper anxiolytic candidate.

Methods

Patients

Twenty-five patients of a private psychiatric clinic (The Fabre Clinic) participated in the two studies. In order to be admitted to the study, each patient had to be 18 to 60 years of age and be a male, or female who would not become pregnant during the study. Each had to be suffering from anxiety for a sufficient time to indicate that spontaneous remission would not occur during the study. Patients could not participate if they were psychotic, had organic CNS diseases, had alcoholism or drug addiction, had significant cardiovascular, hepatic, renal or hematopoietic disease, or had a history of adverse drug reactions or severe plant allergies. The use of psychotropic drugs was prohibited during the study, and the patients were warned against the use of alcohol. Patients participating in the open-label study were required to have a third party to transport them to and from the clinic.

Procedure

Open-Label Study. Five patients suffering from psychoneurotic anxiety participated. Duration of treatment was 28 days preceded by a four-day washout period. No patients were started on active drug until the laboratory results were found to be within the normal range. The dosage was started at 1 mg b.i.d. and adjusted at the discretion of the investigator, but it was not to exceed 10 mg per 24 hours. Dosage was adjusted until anxiety was controlled. The patients visited the clinic at screen and at days 1, 4, 8, 11, 14, 18, 22, 25, and 32. At baseline and on days 8, 11, 18, and 32, the following measures of efficacy were com-

pleted: Self-Rating Symptom Scale, Hamilton Anxiety Rating Scale, Patient's Global Impressions, and Physician's Global Impressions. A physical examination and ECG were completed at baseline and at day 32. Laboratory evaluation (including complete blood count with differential, SMA-12, and urinalysis) was completed at baseline and at days 11, 18, 25, and 32. Standing and supine blood pressures and pulse rates were recorded at each clinic visit.

Double-Blind Study. Twenty patients suffering from psychoneurotic anxiety participated. Duration of treatment was 28 days preceded by a four-day washout period. The dosage of nabilone used was based on information gained in the open-label portion of the study. The patient was administered either nabilone or placebo in a double-blind manner. Half of the patients were on each treatment. Safety and efficacy evaluations were made according to the same schedule as the open-label study.

Results

Open-Label Study

All five patients completed the entire 28 days of the study. The five participants were Caucasian males ages 22 to 35 years (mean 29.4 years). The dosage was adjusted throughout the study for each patient and ranged from 2 to 8 mg a day. The average dose at the end of the study was 2.8 mg a day. All five patients reported side effects, the most common being dry mouth reported by all five patients. Also reported were drowsiness (one patient), feeling slowed down (three patients), feeling spaced out (one patient), headaches (one patient), and dry eyes (one patient). None of the side effects was rated as severe. None of the patients reported euphoria, and apparently none enjoyed a drug "high" from the medication. All patients asked to have their dosage lowered when they began to experience side effects.

An after-before comparison was used to

test for possible changes in the efficacy parameters. The baseline value for each patient was subtracted from the last visit value (visit 8). Using this method, nabilone was found to significantly reduce anxiety as measured by the Hamilton Anxiety Scale total score ($P < 0.001$). Both the somatic anxiety and the psychic anxiety factors of the Hamilton Anxiety Rating Scale were significantly reduced ($P < 0.001$). Examination of the Clinical Global Impressions indicated that all five patients improved on the Global Improvement item and three of the five patients improved on the severity-of-illness item. No statistical tests were performed because of the small sample size.

In addition to the physician's ratings, the patients themselves rated improvement in almost all areas. There was a reduction of most of the items of the 56-item symptom checklist (SCL-56). For the patients' Global Impressions, four of the five rated themselves as improved since they started receiving medication; and, when comparing each visit with the previous visit, four out of five felt an improvement by the fifth visit. No significant changes were found in the before-after analysis of the blood pressure. However, there seemed to be a slight decrease during the first three visits, after which time the blood pressure tended to return to normal levels.

Double-Blind Study

Twenty patients were enrolled. All of the patients on nabilone completed the study. Of the ten patients receiving placebo, five dropped out before completing the study due to lack of relief of their anxiety symptoms. Significantly more people dropped out from the placebo group than from the nabilone group ($P < 0.03$). Nineteen of the patients were Caucasian; one was Black. There were 15 males and five females participating in the study. The patients' ages ranged from 19 to 41 years, with a mean of 29.0 years. This portion of the study utilized

a fixed dose of nabilone which was 1 mg t.i.d., and matching placebo capsules. One patient on nabilone deviated from this dosing regimen and reduced the dosage to 1 mg per day.

The most common side effect reported was dry mouth. Five patients reported this side effect of mild intensity on 19 occasions, nine reported it of moderate intensity on 28 occasions, and four reported it of severe intensity on seven occasions. Dry eyes of mild to moderate intensity was reported by five patients four times. Moderate to severe drowsiness was reported by three patients seven times. One patient reported moderate to severe headaches and one, moderate to severe insomnia. Other side effects reported infrequently were a lump in the throat, nausea, tingling in the toes, red eyes, diarrhea, constipation, and feeling slowed down. In the placebo group, one patient reported muscle weakness, and one reported vascular dilation around the eyes.

Several efficacy parameters were analyzed by analysis of variance. In each case, the baseline measure was subtracted from the subsequent measurements before the analysis was performed. Almost all the efficacy parameters showed nabilone to be significantly superior to placebo. Figure 1 shows the results for the Hamilton Anxiety Scale. This measure showed dramatic improvement as a result of nabilone treatment. The overall score showed nabilone significantly more effective than placebo ($P < 0.001$), the same result pertaining to the factors of somatic anxiety ($P < 0.001$) and psychic anxiety ($P < 0.001$). It can be seen from Fig. 1 that both treatment groups started at about the same baseline ratings on the Hamilton Scale. On the seventh day of the treatment, the nabilone group showed a 50 per cent reduction in anxiety symptomatology, and this reduction persisted throughout the treatment period. The placebo group showed only a slight and insignificant reduction in anxiety.

The efficacy index of the Physician's Global Impressions showed significant

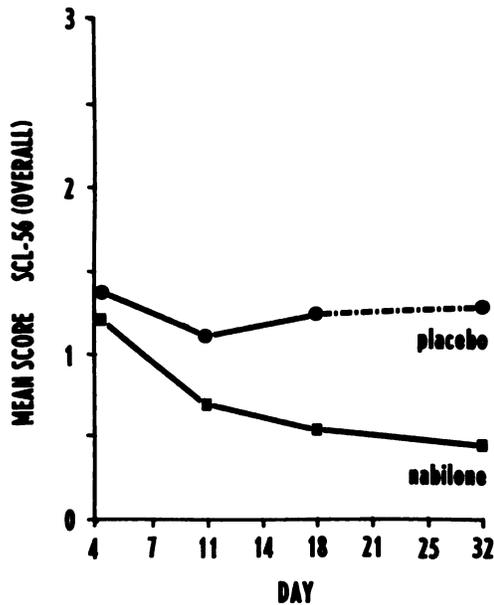


Fig. 1. Effects of nabilone and placebo in the Hamilton Anxiety Rating Scale over a 32-day period. The points on the dashed portion of the placebo curve are mean values of the five placebo-treated patients who did not drop out of the study. All other points are the mean values for ten patients.

improvement for the nabilone group at the $P = 0.002$ level. Overall, there was a downward trend in the severity of symptoms across the duration of the study for the nabilone group but not the placebo group. Alleviation of anxiety occurred quickly, and the patients reported dramatic improvement by day 3.

The results of the patients' self-ratings were consistent with those of the physician. The symptom checklist of 56 items has proved to be a difficult scale with which to measure drug effects on psychiatric symptomatology. However, in this study the difference in efficacy between placebo and nabilone was easily measured. Figure 2 shows the results of the mean score for the anxiety factor of the SCL-56. Anxiety symptoms were greatly reduced by day 11, with a continued decline throughout the treatment period. Here it can be seen that the placebo group showed no decline in

anxiety symptomatology. Figure 3 shows the results of the mean score of the depression factor of the SCL-56. Again the same pattern can be seen: improvement in depression symptomatology by day 11 for the nabilone group and no improvement in depression ratings in the placebo group. Figure 4 shows the results of the overall SCL-56 scores. The trend is the same. A large reduction in overall symptomatology can be seen by day 11 in the nabilone group, and the reduction continued until the end of treatment. The placebo group showed a slight decrease by day 11, with a return to pre-treatment symptomatology after this rating period and continuing throughout the study. Also, individual items of the SCL-56 were improved such as somatization ($P = 0.087$) and interpersonal sensitivity ($P = 0.065$). In fact, changes in all of the items on the SCL-56 were either significant or approaching significance.

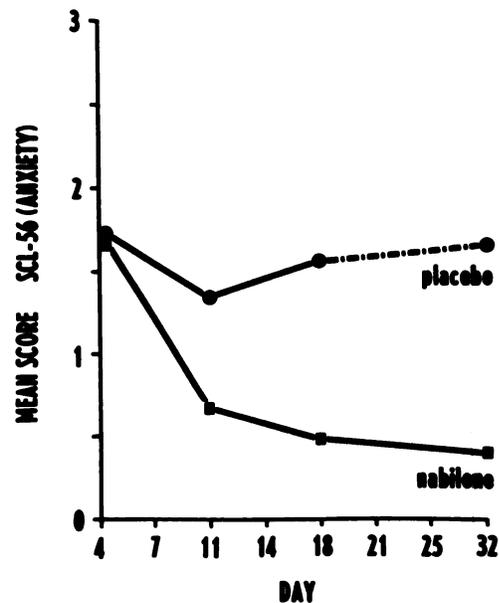


Fig. 2. Effects of nabilone and placebo on the anxiety factor of the 56-item symptom checklist over a 32-day treatment period. The points on the dashed portion of the placebo curve are mean values of the five placebo-treated patients who did not drop out of the study. All other points are the mean values for ten patients.

NABILONE ON ANXIETY

There was a slight but statistically insignificant decrease in blood pressure for the nabilone group during the first few visits, and later this tended to rise to baseline levels. Compared to predrug values, the nabilone group showed a decrease in the systolic blood pressure ($P=0.060$). No changes were noted in the placebo group. There were no other observable effects on the parameters of the physical examination, and nabilone did not alter any value in the clinical chemistry battery.

Discussion

Anecdotal reports support the idea that marihuana is an anxiolytic. It is likely that many users of marihuana use it for its anxiolytic effects. However, research studying the effects of marihuana or THC have not supported this concept.^{7B} These studies have generally shown that THC or marihuana has the effect of accentuating exist-

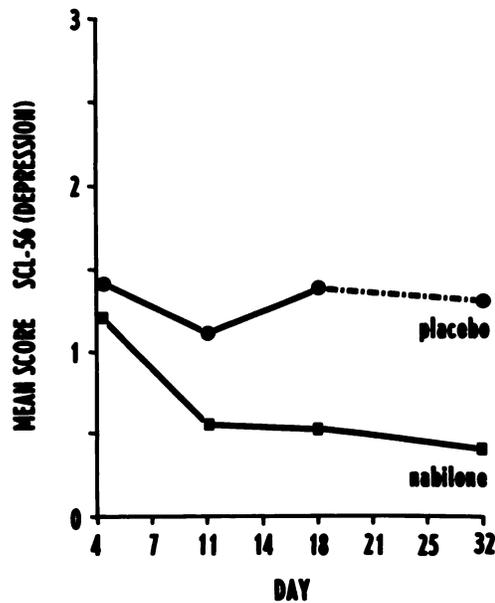


Fig. 3. Effects of nabilone and placebo on the depression factor of the 56-item symptom checklist over a 32-day treatment period. The points on the dashed portion of the placebo curve are mean values of the five placebo-treated patients who did not drop out of the study.

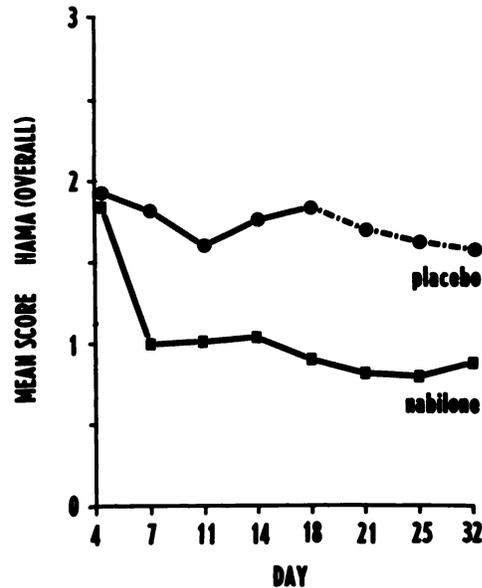


Fig. 4. Effects of nabilone and placebo on the total score of the 56-item symptom checklist over a 32-day treatment period. The points on the dashed portion of the placebo curves are mean values of the five placebo-treated patients who did not drop out of the study. All other points are the mean values for ten patients.

ing feelings and that no relief of anxiety is produced.

Recently, cannabinoid research has focused on the development of synthetic compounds which separate beneficial effects of marihuana from undesirable effects. Nabilone represents one of the first of this class of compounds. Preclinical research indicated that nabilone had anti-anxiety activity.⁴ The results of the studies presented here confirm that nabilone does in fact have anxiolytic activity in man. Our results have in turn been confirmed by Ilaria and Fann working in a Veterans Administration Hospital setting.⁹

Two groups have studied the acute effects of nabilone: one on human subjects with experimentally induced anxiety,¹⁰ and the other on anxious volunteers.¹¹ Both have found that in single doses nabilone is either ineffective or only mildly effective in reducing anxiety. The difference in these results and our own indicate that nabilone takes

some time to develop its anxiolytic effects. It also suggests that nabilone may have a different mechanism of action than the benzodiazepines.

The anxiolytic program with nabilone was terminated by the sponsor after several cases of hallucinosis were reported in cancer patients being treated with nabilone for antiemesis. No hallucinations were reported in our studies.

We feel that at a dose of 1 mg two or three times a day, nabilone is a very effective anxiolytic deserving of further study.

Acknowledgment

The authors acknowledge Dr. Paul Stark of the Eli Lilly Company for his help and suggestions during the planning, performance, and analysis of this study.

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Original Article

Cannabis Use in HIV for Pain and Other Medical Symptoms

Emily Woolridge, MB BS, BSc, Simon Barton, MB BS (Distinction), BSc, FRCP (Ed), FRCP (London), Jonathon Samuel, BSc, Jess Osorio, BSc, Andrew Dougherty, BSc, and Anita Holdcroft, MB ChB, MD, FRCA

Magill Department of Anesthesia, Imperial College London (E.W., A.H.), and HIV/GUM Services (S.B., J.S., J.O., A.D.), Chelsea and Westminster Hospital, London, United Kingdom

Abstract

*Despite the major benefits of antiretroviral therapy on survival during HIV infection, there is an increasing need to manage symptoms and side effects during long-term drug therapy. Cannabis has been reported anecdotally as being beneficial for a number of common symptoms and complications in HIV infections, for example, poor appetite and neuropathy. This study aimed to investigate symptom management with cannabis. Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration. Symptom control using cannabis is widespread in HIV outpatients. A large number of patients reported that cannabis improved symptom control. *J Pain Symptom Manage* 2005;29:358–367. © 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Cannabis, HIV, pain, symptoms

Introduction

HIV or AIDS affects over 40 million people in the world¹ and more than 49,500 in the UK.² Although there is still no cure available for this disease, remarkable improvements in the survival of HIV-infected individuals have been achieved.³ This survival has led to an increasing prevalence of individuals with HIV infection, many on long-term treatment with combinations

of antiretroviral therapies. This has increased the clinical focus on the management of chronic symptoms associated with both HIV and the side effects of antiretroviral medication. Recently, in small sample studies of HIV patients, the medicinal use of cannabis has been documented as a treatment for varied symptoms.^{4–7}

Symptoms associated with HIV occur as both direct and indirect consequences of the disease process and as a side effect of the antiretroviral drugs used in the treatment of the disease. These symptoms include nausea and vomiting, pain (e.g., in a nerve distribution), reduced appetite, weight loss, headaches, diarrhea, constipation, anxiety, and depression. Flu-like symptoms and severe myalgia can result directly

Address reprint requests to: Anita Holdcroft, MB ChB, Magill Department of Anesthesia, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom.

Accepted for publication: July 28, 2004.

from seroconversion early in the disease. Central pain and peripheral neuropathy can occur as a result of viral-mediated neurotoxicity, secondary to either mitochondrial damage, demyelination, or low B₁₂ levels, all of which have been observed in patients with HIV. The inflammation that occurs as a result of the mitochondrial damage can result in HIV-related encephalopathy or HIV-related colitis. Symptoms may also occur secondary to infections or tumors, which have resulted from HIV-related immunosuppression. Examples of this include nausea and dysphagia from esophageal candida, or pain from a gastrointestinal lymphoma. Symptoms commonly occurring as a side effect of HIV treatment include renal colic from nephrolithiasis associated with the protease inhibitor, indinavir; painful peripheral neuropathy from use of stavudine, a nucleoside analogue; or sleep disturbances from the non-nucleoside inhibitor, efavirenz. Thus, a wide range of symptoms can significantly affect the quality of life of individuals living with HIV as a long-term chronic infection.^{8,9}

It has been recognized that cannabinoids such as delta-9-tetrahydrocannabinol (THC), which is now available as a licensed pharmaceutical preparation, can improve appetite and relieve nausea and vomiting.¹⁰ Cannabis plant material not only contains THC but also other cannabinoids, such as cannabidiol (CBD), that may mitigate psychotic mood effects of THC.¹¹

The aim of this study was to measure the patterns and prevalence of cannabis use in patients presenting at a large HIV clinic and to evaluate its beneficial or detrimental effect on symptom control.

Methods

Subjects

Following Ethics Committee approval, HIV-positive patients were recruited into an anonymous cross-sectional questionnaire survey using a single center. The outpatient clinic provided a walk-in service as well as pre-arranged appointments, including pharmacy and phlebotomy sections. All patients entering the clinic were asked to verbally consent to participate in the study. Written consent was not obtained in order to protect patient anonymity. The number of patients who refused to take part

was recorded. Many patients were regular clinic users, had discussed their symptoms with HIV and pain specialists, and were able to distinguish between the various types of pain described on the questionnaire. A researcher was available to answer questions (e.g., on the interpretation of words). Patients completed the questionnaire while waiting and confidentiality was maintained by enumerating the papers without patient identification.

Questionnaire

The questionnaire was piloted to refine its content, word use, and format and then issued to patients attending the clinic. The questionnaire (see Appendix) was designed to contain close-ended questions with defined yes/no or categorical responses. It was divided into sections. The first included demographics (age, sex, number of years with HIV) and a validated scale to measure degree of disability described by Sharrack and Hughes.¹² The second had specific questions concerning the patient's use of cannabis medically to treat symptoms of HIV. These symptoms included those directly related to HIV plus those resulting from their medication. Those who did not use cannabis for medicinal purposes, including those who used it solely for recreation, were not required to continue completing the questionnaire, although their demographic details were recorded. The next section included questions relating to frequency, patterns, and reasons for cannabis use. Then in tabular form, a range of symptoms were listed (Table 1), and against

Table 1
Order of Symptom List in Questionnaire as Scored by Patients for Benefit or Detriment

Lack of appetite
Feeling sick (i.e., nausea)
Tremor
Depression
Anxiety
Weight loss
Weakness
Tiredness
Vision dimness
Slurred speech
Memory loss
Constipation
Headaches
Diarrhea
Pain in muscles
Nerve pain
Tingling
Numbness

each one, the patient was invited to score benefit or detriment as 'much better,' 'little better,' 'unchanged,' 'a little worse,' and 'much worse'. For the symptoms of pain and sensory changes, the questionnaire also contained 'body diagrams', that is, pain maps, so that the patients could mark where they identified their nerve or muscle pain, tingling and numbness.

Analysis

Data from the questionnaires were entered into an Access database (Windows 98 version) and analyzed using the Statistical Package for Social Sciences (SPSS 11.5, SPSS Inc., Chicago). Categorical data comparing the sex differences between the two groups and symptom severity were analyzed using the Fisher's exact test. Because the distribution of age and the number of years with HIV were not normal and had some outliers, the differences in these variables between the two groups were analyzed using the Mann-Whitney U test. Both simple frequency analysis and the sign test were used in assessing the percentage improvement or deterioration in symptoms.

Results

A total of 523 questionnaires were completed from 565 patients approached. This was a 93% response rate. Of those who completed the study, 143 (27%) used cannabis to treat symptoms associated with HIV.

Physical Data

The sex, age, years with HIV, disability, and cannabis user status are shown in Tables 2 and 3.

About 1 in 10 patients were female and few were severely disabled in this outpatient setting. Compared with females, males were statistically significantly likely to be cannabis users ($P < 0.01$) and those who had the disease for longer and were more disabled were also more likely to be users ($P < 0.01$).

When nerve pain was reported on the pain map, it was experienced mainly in the legs, and less in the feet and hands (27, 19, and 15 patients, respectively). Muscle pain was predominantly localized to the legs, but also to the lower back, shoulders and neck (46, 19, and 19 patients, respectively). Tingling and numbness was experienced in the periphery, with the hands and feet being affected (34 and 26 patients, respectively).

Patient Choice of Route and Timing for Symptom Control

Of the 143 patients who had used cannabis to treat HIV symptoms, 107 (75%) were current users. Within the whole group, smoking was the single route of administration in 101 (71%), and was combined with eating and drinking the plant in 39 (27%); ingestion was the only route in 3 (2%). On a day that cannabis was used, 50 patients (36%) would take it once, 33 (23%) twice, 23 (16%) three times, and 35 (24%) four or more times. Most patients (79/143 [55%]) were daily users and 15 (11%) used it weekly. Others reported intermittent administration during the week. Thus, all patients reported using cannabis at least once a week to relieve symptoms.

Throughout the day, the majority of patients (91/143 [64%]) took cannabis after 6 p.m. and

Table 2

	Females $n = 43$ (8%)	Males $n = 480$ (92%)	All Subjects $n = 523$
Age (years) ^a	38 [32–43] (20–65)	39 [35–44] (20–69)	39 [35–44] (20–69)
Years with HIV ^a	6 [2–9] (0–18)	9 [4–13] (0–25)	8 [4–13] (0–25)
Disability ^b			
0	12 (28%)	164 (34%)	176 (34%)
1	14 (33%)	136 (28%)	150 (29%)
2	10 (23%)	100 (21%)	110 (21%)
3	4 (9%)	74 (15%)	78 (15%)
4	3 (7%)	5 (1%)	8 (2%)
5	0	1 (0.2%)	1 (0.2%)
Number that used cannabis to treat symptoms	4/43 (9%)	139/480 (29%)	143/523 (27%)

^aMedian [IQR] (range).

^b0 = none; 1 = mild; 2 = moderate not requiring help from others; 3 = moderate requiring help from others; 4 = severe with almost total loss of function; and 5 = total loss of function.

Table 3
Demographic Differences Between Users and Non-Users of Cannabis for Symptom Control

	Users <i>n</i> = 143	Non-Users <i>n</i> = 380	Statistical Significance
Males:Females	139:4	341:39	<i>P</i> < 0.01
Age ^a	40 [36–44] (26–61)	38 [34–44] (20–69)	<i>P</i> = 0.046
Years with HIV ^a	10 [6–15] (0–25)	7 [3–12] (0–20)	<i>P</i> < 0.01
No disability:Disability	17:126	159:221	<i>P</i> < 0.01

^aMedian [IQR] (range).

before midnight. However, an overlapping group (66/143 [46%]) also reported use at any time if necessary. The reasons for taking the cannabis at these times were reported in a structured format, as detailed in Table 4. A number of reasons related to the time of administration, not least of which was recreational use together with medicinal use. Relief of symptoms of anxiety and depression was common, as was general symptom relief. The reported use for relaxation may reflect the time at which it was taken, namely, during the evening.

Effect on Symptoms

A lack of appetite was the most frequent symptom reported (Table 5) and 97% experienced improvement with cannabis use. Pain was the next most frequent, being present in 45% of patients and improved in 94% of them. The collective results demonstrated statistically significant improvement in half or more patients in symptoms of nausea, anxiety, nerve pain, depression, tingling, numbness, weight loss, headaches, tremor, constipation, and tiredness. Symptoms that were not improved included weakness and slurred speech, and statistically significant memory deterioration was recorded in 47% of users.

Discussion

The demographic characteristics of our cohort of patients (male:female, 11.2:1) is comparable with the UK population of HIV-positive

patients, which has a male:female ratio of 11.5:1. In addition, their ages and duration of HIV disease were comparable with the general UK data for such patients.¹³ Our sample of 523 patients has the highest response rate and is the largest study of its kind. It compares with previous studies, which have had samples ranging from 72 subjects⁷ to 442.⁶ This detailed report of cannabis use for symptom control in a clinically significantly large group of patients can form the basis for more extensive investigations using purified and standardized cannabis extracts.

Despite the fact that cannabis is still illegal, its use for medical purposes appears to be quite widespread. A report from the British Medical Association¹⁴ stated “many normally law abiding citizens—probably many thousands in the developed world” use cannabis illegally for therapy. Wesner¹⁵ reported from an anonymous mail survey of 123 HIV-positive patients in Honolulu that 36.9% of them used cannabis for therapeutic reasons. Approximately one-quarter of 228 HIV-positive men in the Sydney Men and Sexual Health study reported therapeutic use of cannabis.¹⁶ Thirty-two percent (32%) of 72 patients at a clinic in Alabama reported the medical use of marijuana.⁷ These results are comparable to a more recent study carried out in Northern California, in which 33.3% of HIV-positive patients who responded to an anonymous mailed questionnaire used cannabis to treat symptoms associated with their disease.⁶ Our study expanded these findings in a large city clinic population by focusing on the patient’s perceived improvement or worsening of symptoms for which cannabis was considered the origin.

The large number of patients using cannabis as medicinal therapy for symptoms related to HIV raises a number of issues. First, patients are being left with no alternative but to use a non-medical source of supply, which has the

Table 4
Reasons for Using Cannabis

Purpose	<i>n</i>	%
Treat symptoms	77	54
Aid relaxation	121	85
Reduce anxiety	94	66
Relieve depression	75	52
Reduce symptom frequency	29	20
Increase energy levels	15	11
For a ‘high’	62	43

Table 5
Effect of Cannabis on Complaint of Symptoms in 143 HIV Patients

Symptom	Number of Complaints	% Responding					P-value
		Much Better	Little Better	No Change	Little Worse	Much Worse	
Lack of appetite	111	79	18	2	0	1	0.000
Pain in muscles	65	63	31	6	0	0	0.000
Nausea	62	56	37	3	2	2	0.000
Anxiety	98	64	29	3	2	2	0.000
Nerve pain	53	51	40	9	0	0	0.000
Depression	94	56	30	9	4	1	0.000
Tingling	46	37	48	9	7	0	0.000
Numbness	42	36	36	24	5	0	0.000
Weight loss	62	45	24	31	0	0	0.000
Headaches	46	35	30	33	2	0	0.000
Tremor	24	37	29	21	13	0	0.004
Constipation	24	21	29	46	4	0	0.003
Tiredness	60	17	33	33	15	2	0.002
Diarrhea	48	13	23	56	6	2	0.007
Vision dimness	22	9	27	55	9	0	0.109
Weakness	48	10	21	54	15	0	0.134
Memory loss	38	13	5	34	34	13	0.043
Slurred speech	9	11	0	78	11	0	1.00

Note: In ranked order of those demonstrating improvement (recorded as % much better, little better) in comparison to those recorded with no change, little worse, or much worse. The *P*-value in the last column is the exact 2-sided *P*-value for the sign test of no change.

potential for heterogeneity of active cannabinoids, toxic contaminants, inappropriate dose, and drug misuse. Second, if part of the plant material has therapeutic efficacy, the source of this material should be standardized and subjected to clinical trials so that safe and effective use is advocated. Third, the patient is unlikely to divulge cannabis use to their medical team, so that potential drug interactions with prescribed antiretroviral medications may be occurring. In addition, in this study, the number of purely recreational users was not determined so that the overall incidence of drug interactions may be far greater. The type of drug interactions to be considered include loss of cognitive function because it is well-recognized that this is an effect of both cannabis¹⁷ and antiretroviral drugs such as efavirenz.¹⁸ Certainly, the loss of memory reported by these patients is of clinical significance, particularly in the methodological design of clinical trials, and if it is the result of combining preparations, this may be investigated using known standardized cannabinoid therapies. This approach may be one way to reduce additive effects and prevent patients being subject to the effects of unpredictable concentrations of illicit drugs.

The positive responses to symptom control recorded in this study, as exemplified in Table 5, suggest that it is highly probable that cannabinoid medications have a medicinal role in this condition for a number of reasons. First, they

are reported by patients to improve appetite, reduce weight loss, and alleviate nausea.^{19–23} These effects have been recognized and synthetic THC (dronabinol) is licensed for use in the U.S. for this indication. However, no direct comparison has been attempted with a cannabis plant extract that will contain not only THC but also other cannabinoids, of which CBD is reputed to reduce the adverse effects of THC.²⁴ Secondly, pain relief appears to be significant in cannabis users, thereby suggesting a potential target for investigation in the use of cannabinoids as analgesics in HIV patients.

Patients have reported various forms of pain with HIV, such as muscular and neuropathic pain, and these were characterized in the pain maps drawn by the patients. Currently available analgesic drugs have limited efficacy, particularly for neuropathic pain.²⁵ Clearly, there is a need to develop alternative analgesic agents, such as cannabinoids, to improve the choice of therapies. There is animal evidence that cannabinoids have analgesic effects that operate in models of hyperalgesia and allodynia, both indicators of neuropathic pain states,^{26,27} and the discovery of the endogenous cannabinoid system has led scientists to explore the role of endocannabinoids in chronic pain models.^{28,29} However, in clinical practice the choice of natural or synthetic phyto- or endo-cannabinoids for clinical trials is very limited. There have been several anecdotal and clinical trial reports that

cannabis plant extract and synthetic THC and related analogues produce pain relief in humans.^{30–33} For this present select group of HIV patients, given the reported symptoms experienced using cannabis plant material, there is a strong concern from the medical community managing these patients to limit adverse side effects from self-administered drugs and to provide cannabinoids in a formulation and dosing schedule that avoids harm to the patient. For example, there is strong evidence that the smoking route of administration of cannabis is not safe long-term because of the carcinogenic properties of a cannabis cigarette.³⁴

A pattern of cannabis use emerges from this study that is regular, ongoing, and treats the symptoms of HIV patients to their satisfaction. Given the sedative properties of cannabis, it is important to assess whether evening dosing for cannabinoid therapies is more useful or appropriate. Its sedative effects may be helpful at this time but none were reported as predominant. Presumably there is tolerance to these types of effects.²⁹ More importantly, reduction of pain, anxiety, and gastrointestinal upset appears to be the constellation of symptom control sought by these HIV patients, as shown in Tables 4 and 5.

In relation to HIV, there have been anecdotal reports³⁵ of patients who were already recreational users of cannabis reporting that it improved certain symptoms, such as loss of appetite and nausea, as well as pain and general well being. A small, uncontrolled study of 10 symptomatic AIDS patients reported that dronabinol might be effective in reducing nausea and increasing appetite.¹⁰ Where patients are also medicating with antiretroviral agents, the combination of cannabis and protease inhibitors may be detrimental by altering viral loads. Thus, the effect of smoking on the viral load of HIV-infected patients was investigated by a short-term randomized placebo controlled trial.³⁶ No adverse effects of either therapy were measured with respect to RNA levels, CD4⁺ and CD8⁺ cell counts, or protease inhibitor levels. This brief trial suggests that there are no obvious harmful effects, but these need to be determined using an appropriate route of drug administration and a longer-term study.

There is accumulating evidence that suggests that cannabinoids have therapeutic applications in a variety of neurodegenerative diseases,

such as multiple sclerosis,^{37,38} Huntington's disease,³⁹ and brain injury.⁴⁰ So far, in terms of HIV, the evidence for therapeutic efficacy of cannabinoids is still mainly anecdotal. We have sought to establish if an improvement from cannabis use, albeit self-administered and not standardized, is seen in symptoms such as pain, appetite, and nausea in a large sample of HIV patients. To do this, we expanded on previous research by determining specifically the variety and groups of symptoms that patients select to modify by their use of cannabis. We also secured a therapeutic timetable in order to predict the frequency of drug administration for the patient's selected symptoms. These results will be important in the design of a randomized, placebo-controlled clinical trial comparing conventional treatments to cannabis for symptoms of HIV.

Acknowledgments

The authors thank Dr. Elena Kulinskaya for statistical advice and Dr. Sarah Cox, Dr. Andrew Rice, and the staff at the Kobler Clinic, St. Stephen's Center.

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Appendix
Questionnaire

HIV Symptoms and the Use of Cannabis

This questionnaire is designed to establish the current use of cannabis for the management of symptoms from HIV in our patients. We would be grateful for some personal details (but not details of identification) and your past and present experiences (if any) with cannabis.

Please complete the following:

General Details:

Sex: MALE/FEMALE (encircle as necessary)

Age:years

Number of years with HIV:

Degree of Disability

Please choose ONE of the following statements which best describes how severely you are affected by the HIV disease, and how it affects your activities of daily living:

- None
- Mild symptoms
- Moderate symptoms—not requiring help from others
- Moderate symptoms—requiring help from others
- Severe symptoms—almost total loss of function
- Total loss of function

Cannabis use

Have you ever used cannabis to relieve your symptoms (as listed below) of HIV? Y/N

If “NO” we thank you for answering this questionnaire and you are not required to complete any more of the questionnaire.

If “YES” please complete the following details:

How do you take the cannabis?

- Smoke Y/N
- Drink Y/N
- Eat Y/N
- Other (state).....

How many years have you used cannabis relieve some of your symptoms?.....years

How many times a day do you use cannabis?.....

How many days a week do you take cannabis?.....

When do you take cannabis: [*Please choose only ONE*]

After 6 pm and before midnight	Y/N
Between 6 am and midday	Y/N
Midday to 6 pm	Y/N
At any time when necessary	Y/N
Just before going to bed	Y/N
At regular intervals during the day	Y/N

Do you take cannabis to: [*You may choose MORE THAN ONE*]

Relieve symptoms	Y/N
Aid relaxation	Y/N
Relieve anxiety	Y/N
Relieve depression	Y/N
Reduce symptom frequency	Y/N
Obtain energy	Y/N
To get a 'high' / Recreational	Y/N

For each symptom in the left-hand column state if the symptom is now present. Then mark for each symptom, whether past or present, its response to cannabis use, i.e., better or worse. Diagrams are provided below for the question relating to sites of pain, etc.

Symptom (past or present)	Present	Response to cannabis <i>[Please tick ONE box]</i>				
	Y/N	Much better	Little better	Not changed	Little worse	Much worse
Lack of appetite						
Feeling sick, i.e., Nausea						
Anxiety						
Depression						
Tremor						
Headaches						
Weight loss						
Weakness						
Tiredness						
Vision dimness						
Slurred speech						
Tremor						
Memory loss						
Constipation						
Diarrhea						
Muscle pain (please mark on Diagram 1 where you are affected by this)						
Nerve pain (please mark on Diagram 2 where in your body this is)						
Tingling (draw on Diagram 3 where this is)						
Numbness (draw on Diagram 4 where this is)						
Others (please state)						

N.B. Please do not forget to fill in the body diagrams on the next page if you suffer from MUSCLE PAIN, NERVE PAIN, TINGLING OR NUMBNESS.

Once completed please hand over this questionnaire to the reception desk.

THANK YOU.

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

Perm J 2016 Fall;20(4):16-005

E-pub: 10/12/2016

<http://dx.doi.org/10.7812/TPP/16-005>

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.

Acknowledgments

CannaVest Corp, San Diego, CA, which had no involvement in the case study or distribution of the product, provided the CBD oil that was administered to the patient. No financial support was provided.

Kathleen Loudon, ELS, of Loudon Health Communications provided editorial assistance.

How to Cite this Article

Shannon S, Oplia-Lehman J. Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of posttraumatic stress disorder: A case report. *Perm J* 2016 Fall;20(4):16-005. DOI: <http://dx.doi.org/10.7812/TPP/16-005>.

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.

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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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Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo



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

ARTICLE INFO

Article history:

Received 18 April 2013

Received in revised form 10 August 2013

Accepted 30 August 2013

Keywords:

Cannabis

Medical marijuana

Access to cannabis

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

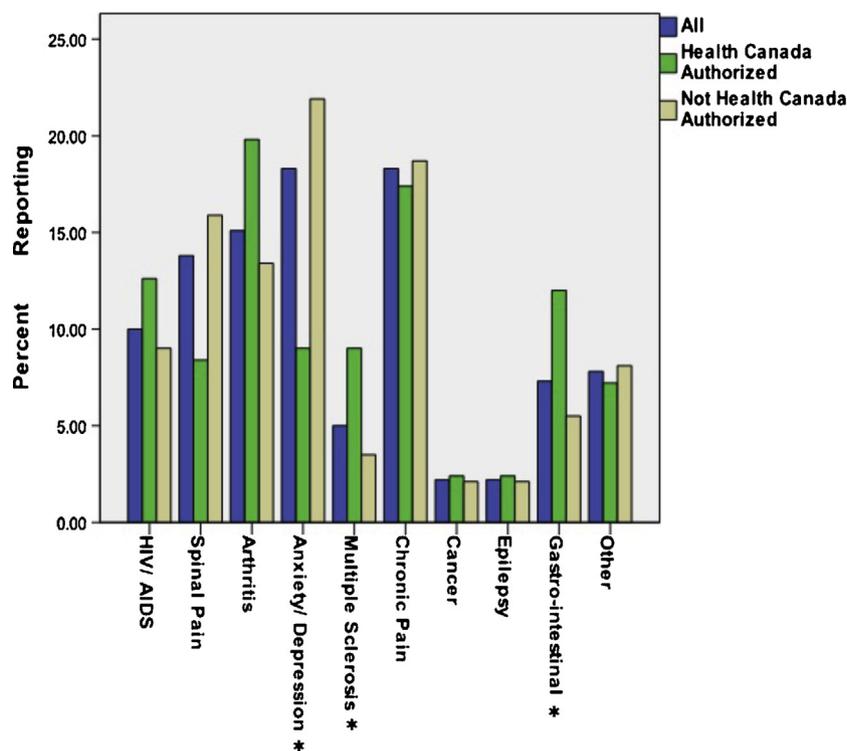


Fig. 1. Primary medical conditions treated with cannabis by authorization. *Note:* Sleep Disorders, Attention Deficit Disorder, Fibromyalgia, Hepatitis C, Parkinson’s Disease, Wilson’s Disease, Scleroderma, Tourette’s Syndrome, and unspecified Psychotic Disorder Conditions each comprised less than 2% 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.

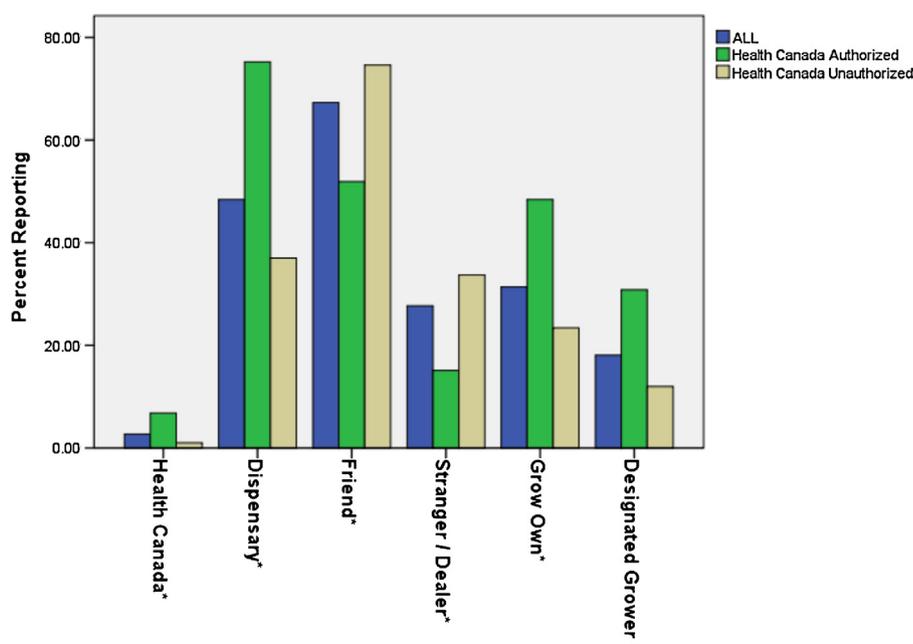


Fig. 2. Modes of Access. Note: * = difference between proportion Health Canada Authorized and Unauthorized $p < .01$; $n = 498$.

$p < .01$), 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.

Acknowledgements

This research was supported by a grant from the UBC Institute for Healthy Living and Chronic Disease Prevention. The authors thank the people who took the time to respond to the survey. We would also like to thank Ben Atkinson, Kim Crosby and Megan Hiles for their contribution to data collection and management, and Brian Emerson for providing valuable feedback on the manuscript.

Conflict of interest statement

None of the authors have any conflicts of interest with regard to the contents of this manuscript. Access.

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Patterns of cannabis use among patients with multiple sclerosis

A.J. Clark, MD, FRCPC; M.A. Ware, MBBS, MRCP(UK); E. Yazer, BSc; T.J. Murray, FRCPC; and M.E. Lynch, MD, FRCPC

Abstract—To estimate the patterns and prevalence of cannabis use among patients with multiple sclerosis (MS), 220 patients were surveyed in Halifax, Nova Scotia. Seventy-two subjects (36%) reported ever having used cannabis for any purpose; 29 respondents (14%) reported continuing use of cannabis for symptom treatment. Medical cannabis use was associated with male gender, tobacco use, and recreational cannabis use. The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain.

NEUROLOGY 2004;62:2098–2100

Published reports spanning 100 years suggest that people with spasticity may experience relief with cannabis.¹ The epidemiology of cannabis use among patients with multiple sclerosis (MS) is not well described. A recent postal survey (60% response rate) of 420 patients with MS from southern Alberta, Canada in 2000 estimated that 16% of patients had used cannabis for therapeutic purposes.² We report the results of a 2002 survey in which we evaluated the patterns and prevalence of cannabis use in Halifax, Nova Scotia.

Methods. A cross-sectional questionnaire-based survey was designed to collect information on demographics (age, gender, years with MS, and medications used) and medicinal and recreational cannabis use. Subjective cannabis effects were documented using 5-point Likert scales on a range of symptoms, including spasticity, pain, mobility, sleep, and mood. Side effects experienced were recorded. Information on doses used, means of administration, frequency, and duration of use was collected. In addition, strength of commitment to use cannabis in the future was recorded. The Queen Elizabeth II Health Sciences Centre Research Ethics Committee approved the study protocol and questionnaire.

A sample size of 144 was calculated to be sufficient to detect an estimated prevalence of 10% with a 2.5% standard error. To account for 20% refusals and those who incorrectly filled in forms, we aimed to administer 175 questionnaires; 220 forms were prepared and administered at the study site.

Data were double entered and validated using standard procedures by a central data management agency (GEREQ, Quebec, Canada). Missing values constituting <5% of the total were not included in summary statistics. Analyses were conducted using statistical software (Stata version 8.0, Houston, TX).

Data are presented as summary statistics (means and medians) as appropriate. Ordered categorical data (e.g., degree of relief and severity of side effects) were summarized as proportions (e.g., number of patients indicating moderate to complete relief com-

pared with total responses). The prevalence and patterns of cannabis use were estimated and analyzed by cross-tabulating the responses from medicinal cannabis users and others with respect to demographic characteristics. Continuous normally distributed data were compared using Student's *t*-test. Categorical data were compared using Pearson χ^2 tests. Ordered categorical data were analyzed using Mantel-Haenszel tests. Significance was set at the 95% level, and all tests were two sided.

Results. Two hundred five questionnaires were returned (93% response rate). The demographic characteristics of the subjects are shown in table 1. Subjects are shown categorized by their medicinal cannabis use status. Ever-use of cannabis for medical purposes was found to be significantly associated with male gender ($p = 0.03$), use of tobacco ($p < 0.001$), and recreational use of cannabis ($p = 0.009$).

Perceived effects and side effects. The 34 medical users rated the overall effectiveness of cannabis; more than half of these subjects reported cannabis as being very effective (2, not effective; 2, slightly; 10, somewhat; and 20, very effective). The perceived effectiveness of cannabis on individual symptoms is shown in table 2. Cannabis use was reported to reduce the number of doses of routine medication taken by 14 subjects, whereas 19 reported that cannabis had no effect on the number of doses of routine medication used.

Of the 34 medical cannabis users, 15 reported no overall side effects, 10 reported very mild side effects, 8 reported moderate side effects, and 1 reported strong side effects. No subject reported severe side effects. The most common side effect was "high," which was reported by 24 subjects, followed by drowsiness by 20, dry mouth by 14, paranoia by 3, anxiety by 3, and palpitations by 3.

See also pages 1924 and 2095

From Dalhousie University (Drs. Clark, Murray, and Lynch, E. Yazer), Halifax, Nova Scotia, Canada; and McGill University (Dr. Ware), Montreal, Quebec, Canada.

J.C. and M.W. contributed equally to this manuscript.

Supported by a summer research student award from the Department of Anesthesia, Dalhousie University (E.Y.). M.W. is supported by the Fonds de la Recherche en Santé du Québec (FRSQ) and the Canadian Institutes of Health Research (CIHR).

Received November 11, 2003. Accepted in final form March 2, 2004.

Address correspondence and reprint requests to Dr. Mark A. Ware, E19.145, Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada; e-mail: mark.ware@muhc.mcgill.ca

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Table 1 Demographic characteristics of 205 patients with multiple sclerosis by cannabis use

Variable	Medical cannabis use								p Value
	Ever, n = 34		Never, n = 77		Missing, n = 94		Total		
	n	%	n	%	n	%	n	%	
Age in years									0.1
≤45 years	23	21	43	39	45	40	111	56	
>45 years	11	12	32	36	45	51	88	44	
Gender									0.04
Male	10	30	13	39	10	30	33	16	
Female	24	14	63	37	82	49	169	84	
Tobacco use									<0.001
Yes	24	39	21	34	16	26	61	30	
No	9	6	55	39	76	54	140	70	
Duration of MS									0.7
≤10 years	17	15	43	39	51	46	111	56	
>10 years	17	20	32	37	38	44	87	43	
Use of medication for pain/ mood/sleep/spasms									0.5
Yes	22	18	44	37	53	45	119	59	
No	12	15	31	38	39	48	82	41	
Recreational use of cannabis									0.009
Yes	19	26	53	72	2	3	74	36	
No	14	19	53	89	3	8	131	64	
Missing	1	1	5	5	89	94			

Nine subjects gave reasons why they had stopped using cannabis: three stated that obtaining it was too risky; two said cannabis had no effect at all; one reported that side effects were intolerable; and one said that symptoms had improved. No subject stated that symptoms got worse with cannabis use.

Patterns of cannabis use. Of 34 medical cannabis users, 15 reported only rare use, whereas 7 reported weekly use, 4 reported daily use, and 8 reported use more than once per day. Seventeen subjects had used cannabis in the past 24 hours; 4 had used in the past week; 3 had used in the past month; 5 had used in the past year; and 5 had not used in more than a year.

Thirty-two subjects gave information on single-dose

size: the most common was an entire joint (14 subjects); three or four puffs at a dose was reported by 13 subjects; and one to two puffs was reported by 4 subjects. One subject stated that he smoked more than one joint per dose. Of the 12 who consumed cannabis orally, 11 stated that they used <1 g at each dose. The most common time of use was at night (29 subjects), followed by late afternoon (22), early afternoon (8), before noon (7), and morning (6).

Discussion. This survey demonstrates a prevalence of current medicinal cannabis use among patients seeking treatment at the MS clinic in Nova Scotia of 14%. This is consistent with data recently published from Alberta, Canada, which found a current use prevalence of 16%.² Medical use is reportedly effective for pain, stress, sleep, mood, and muscle spasm, consistent with reports from the United Kingdom and the United States,³ as well as Canada.² The use of cannabis for stress and anxiety is reported in other populations, such as patients with HIV/AIDS and chronic noncancer pain, and emphasizes the need to better address these symptoms in clinical practice.⁴

Clinical trials of cannabinoids in MS have not been consistent in demonstrating beneficial effects. One small randomized controlled trial in 13 patients with MS found that doses of tetrahydrocannabinol (THC) >7.5 mg reduced patient reports of spasticity compared with placebo.⁵ Reductions in tremor⁶ and

Table 2 Self-reported effects of cannabis on multiple sclerosis symptoms by 34 medicinal cannabis users

Symptom	n	None-mild relief	Moderate-complete relief
Stress	21	1	20
Sleep	18	1	17
Stiffness	17	1	16
Mood	16	0	16
Spasm	15	1	14
Pain	12	2	10
Weight loss	5	1	4

pendular nystagmus⁷ during cannabis smoking have also been observed.

In contrast, cannabis (1.54% THC) increased postural tracking errors among 10 patients with MS and 10 healthy control subjects, especially in the patients with MS.⁸ In a recent randomized controlled trial of 16 patients comparing an oral cannabis extract with oral THC and placebo, cannabinoid treatment did not reduce spasticity or improve subjective impressions.⁹

A large randomized controlled trial (n = 660) recently compared the effects of oral cannabis extracts with pure oral THC and placebo. The study found no difference with respect to the primary outcome measure (modified Ashworth score) but did note significant subjective improvements in pain, spasm, and sleep.¹⁰

In the meantime, patients with MS continue to use cannabis to manage their symptoms. What can we learn from these patients? First, that pain and spasticity are not the only reasons for use, and the effects of cannabis on mood, sleep, and stress are important areas of therapeutic need and should be addressed in clinical trials. Second, there is a wide variance in doses used. Our study found doses ranging from single puffs to >1 g at a time. This may be explained in part by different potencies of available cannabis, with lower-potency preparations requiring larger doses, or by variation between individuals in tolerability or symptom severity. Clinical trials of cannabis for MS will need to include early dose-finding phases and allow for considerable intersubject variability in dose adjustments. Third, cannabis appears to be well tolerated, although some subjects experienced intolerable side effects and deterioration

of symptoms. Access to cannabis emerged as an important obstacle in the use of this drug for medical purposes.

In conclusion, the current study found that patients with MS use cannabis for a range of symptoms. Health care providers should ask about, and be prepared to discuss, the use of this drug with their patients. Coupled with emerging evidence regarding the subjective effectiveness of cannabis on MS symptomatology, further exploration of the utility of cannabinoids in MS is warranted.

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Neurology[®]

Patterns of cannabis use among patients with multiple sclerosis

A. J. Clark, M. A. Ware, E. Yazer, et al.

Neurology 2004;62;2098-2100

DOI 10.1212/01.WNL.0000127707.07621.72

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Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting

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.

Disclosures: The authors report no commercial or financial interests in regard to this article.

Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

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 psycho-neuroimmunology 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 Δ⁹-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 PPARα and PPARγ 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-

Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

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 cannabinol (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

Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

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;

Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

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													

Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

	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.

Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

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-

Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

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.

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Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting

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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

Received 8 June 2016; Revised 29 September 2016; Accepted 10 October 2016

Academic Editor: Jan Aasly

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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 CB1-related mechanism [73]. CBD is also an inverse agonist of CB2 receptors. CBD can counteract some of the functional consequences of CB1 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 CB1 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 CB1 receptors and the endocannabinoid ligands [113]. This could explain the potential of CB1 receptor ligands in alleviating common PD symptoms.

In the brain, CB1 receptors are expressed by GABAergic neurons innervating the external and internal segments of the globus pallidus and the substantia nigra [114–116]. CB1 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, CB1 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 CB1 receptors, levels of endogenous ligands, and CB1 receptor binding in the basal ganglia [119–122]. Endogenous cannabinoids activate CB1 receptors on presynaptic axons and reduce neurotransmitter and glutamate release, working as retrograde synaptic messengers released from postsynaptic neurons [123]. Similarly, activation of CB1 receptors inhibits both glutamate release from substantia nigra afferents and GABA release from striatal afferents. At the same time, activation of presynaptic CB1 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 CB1, D1, and D2 dopamine receptors are localized in the striatum [114, 115]. In animal models, CB1 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 CB1 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.

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Journal of Psychoactive Drugs

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/ujpd20>

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William D. Troutt N.M.D.^a & Matthew D. DiDonato Ph.D.^a

^a Medical Marijuana Research Institute, Mesa, AZ

Published online: 28 Aug 2015.



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To cite this article: William D. Troutt N.M.D. & Matthew D. DiDonato Ph.D. (2015): Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization, Journal of Psychoactive Drugs, DOI: [10.1080/02791072.2015.1074766](https://doi.org/10.1080/02791072.2015.1074766)

To link to this article: <http://dx.doi.org/10.1080/02791072.2015.1074766>

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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.

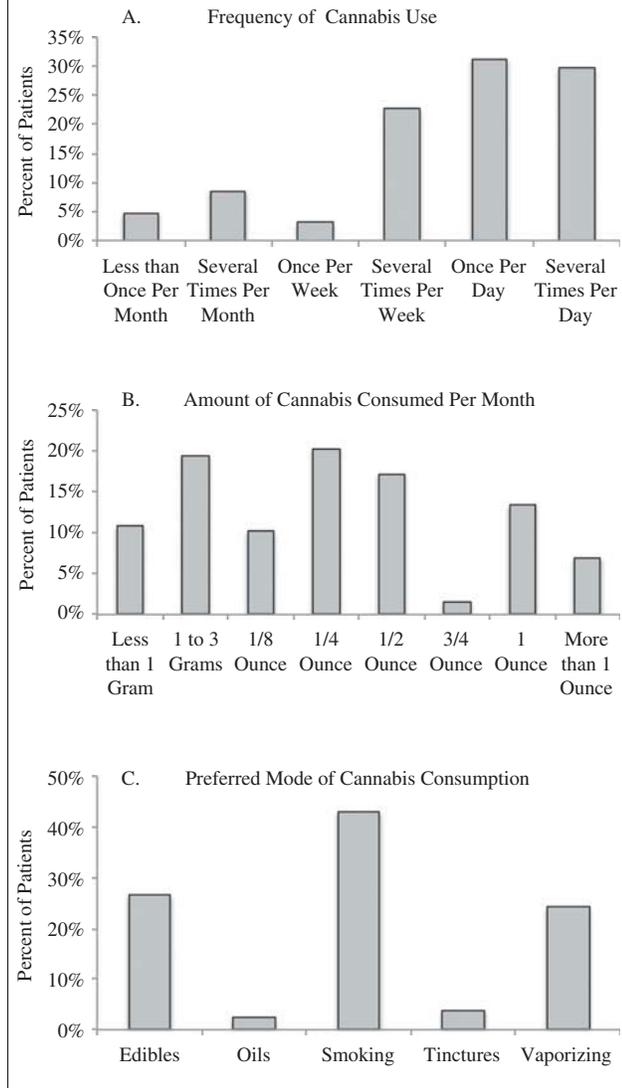
Perceived Effects of Medical Cannabis Legalization

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

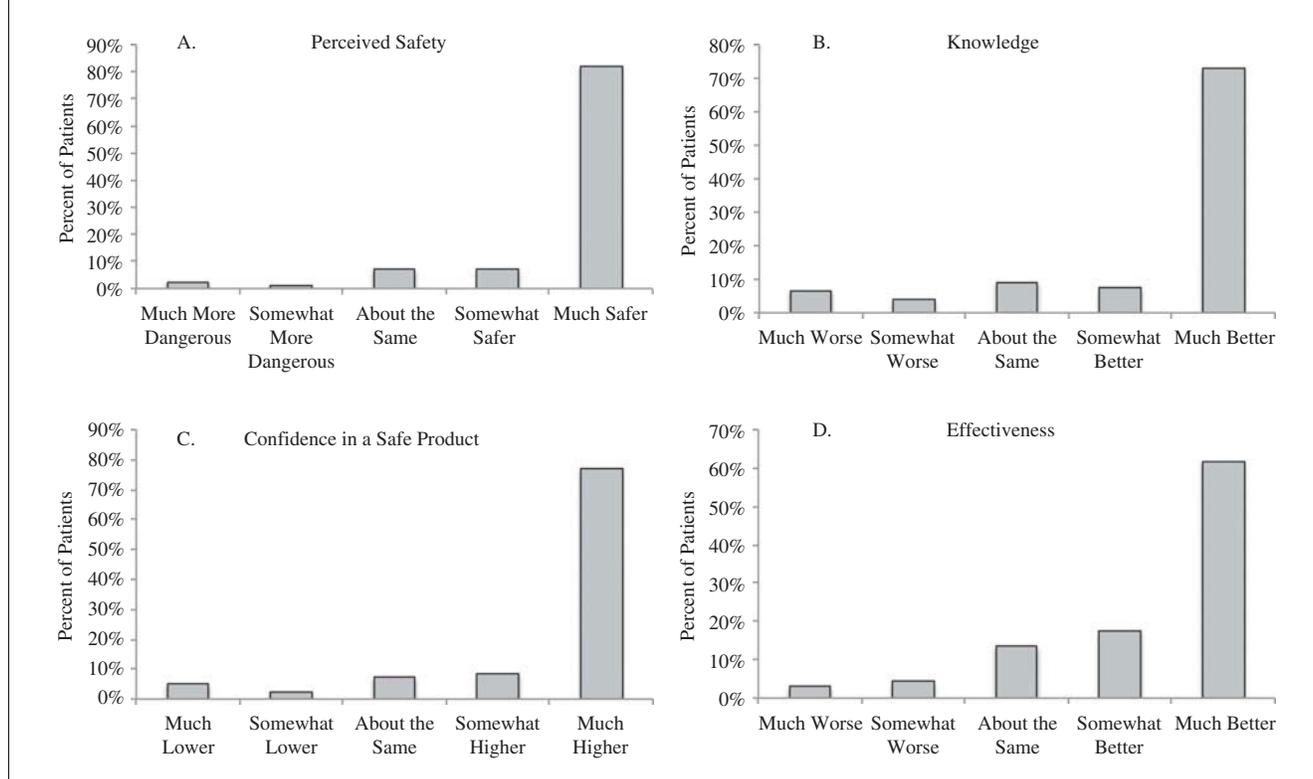
Consistent with research in other states (Bonn-Miller et al. 2014; Aggarwal et al. 2013; Ilgen et al. 2013; Nunberg et al. 2011; Reinerman et al. 2011; Aggarwal et al. 2009; Reiman 2009; O’Connell and Bou-Matar 2007; Harris et al. 2000), participants in the present study were mostly White men. Average 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.

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RESEARCH

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It can't hurt to ask; a patient-centered quality of service assessment of health Canada's medical cannabis policy and program

Philippe Lucas

Abstract

Background: In 2001 Health Canada responded to a series of Ontario court decisions by creating the Marihuana Medical Access Division (MMAD) and the Marihuana Medical Access Regulations (MMAR). Although Health Canada has conducted a small number of stakeholder consultations, the federal government has never polled federally authorized cannabis patients. This study is an attempt to learn more about patient needs, challenges and experiences with the MMAD.

Methods: Launched in the spring of 2007, *Quality of Service Assessment of Health Canada's Medical Cannabis Policy and Program* pairs a 50 question online survey addressing the personal experiences of patients in the federal cannabis program with 25 semi-guided interviews. Data gathering for this study took place from April 2007 to Jan. 2008, eventually garnering survey responses from 100 federally-authorized users, which at the time represented about 5% of the patients enrolled in Health Canada's program. This paper presents the results of the survey portion of the study.

Results: 8% of respondents report getting their cannabis from Health Canada, while 66% grow it for themselves. >50% report that they frequent compassion clubs or dispensaries, which remain illegal and unregulated in Canada. 81% of patients would chose certified organic methods of cultivation; >90% state that not all strains are equally effective at relieving symptoms, and 97% would prefer to obtain cannabis from a source where multiple strains are available. Of the 48 patients polled that had tried the Health Canada cannabis supply, >75% rank it as either "1" or "2" on a scale of 1-10 (with "1" being "very poor", and 10 being "excellent").

Discussion: 72% of respondents report they are either "somewhat" or "totally unsatisfied" with Canada's medical cannabis program. These survey results and relevant court decisions suggest that the MMAR are not meeting the needs of most of the nation's medical cannabis patient community. It is hoped this research will help inform policy changes that will better address the needs of Canada's critically and chronically ill medical cannabis patient population, including the integration of community-based dispensaries into this novel healthcare delivery model.

Keywords: medical cannabis, Marihuana Medical Access Regulations, Health Canada, cannabis dispensary

Background

According to the United Nations Office for Drug Control and Crime Prevention (2001) [1] cannabis is the most popular illicit substance in the world. Despite the high rate of recreational use and over 5000 years of medical use, there has never been a substantiated case

of death resulting from cannabis overdose [2]. However, the therapeutic use of cannabis remains highly controversial, and only a few Western nations have introduced policies or programs to allow legal access to medical cannabis.

The Canadian government currently allows for limited access to medical cannabis through the Marihuana Medical Access Regulations (MMAR), which are administered by Health Canada's Marihuana Medical Access Division (MMAD). These court-ordered regulations are

Correspondence: philippe.lucas1969@gmail.com
Center for Addictions Research of BC, University of Victoria, Technology Enterprise Facility, Room 273, 2300 McKenzie Ave, Victoria, BC, V8P 5C2, Canada

the source of much criticism by end-users and advocates, and have been found by courts to be unconstitutional in a number of decisions for unnecessarily limiting access to legal protection and a safe supply of cannabis [3-6].

Initially established in response to patient needs and ineffective or non-existent federal medical cannabis policies, community-based medical cannabis dispensaries have become the main suppliers of medical cannabis in both Canada and in many of the 14 U.S. states that have legalized the medical use of cannabis [3,7]. In Canada, community-based dispensaries, otherwise known as "compassion clubs" currently supply over 30,000 critically or chronically ill Canadians with medical cannabis [8]. Although Canadian dispensaries continue to operate without legal sanction or protection, recent research suggests that this patient-centered healthcare delivery model builds social capital and provide patients with a safe supply of cannabis within a supportive environment that's conducive to healing [3,7,5].

A Brief History of Cannabis as a Medicine

The medical use of cannabis can be traced back at least 5000 years. The oldest reports originate in China and Egypt. It appears in a medical context in the Vedas, India's oldest religious text, and there are reports of its use as a medicine from fragments of Assyrian texts dating back to 700 B.C. The famous Chinese doctor Hua T'uo (approx. 100 A.D.) reportedly made use of a wine and cannabis mixture as an anesthetic for surgical operations [9].

There are numerous reports of the medicinal properties of cannabis from early in the nineteenth century, the most famous of which is an 1839 report titled "on the Preparations of the Indian Hemp, or Gunjah" by the Irish doctor William B. O'Shaughnessy in which he describes diverse applications for cannabis, including rheumatism, rabies, cholera, tetanus, cramps and delirium tremens [10]. A few years later Ernst Freiherr von Bibra published the renown "Narcotics and the Human Being", devoting thirty pages to the therapeutic use of cannabis preparations and hashish [11].

By the late 19th Century, cannabis-based preparations were manufactured and marketed by Burroughs-Wellcome & Co. in England; and Bristol-Meyers Squibb, Parke-Davis, and Eli Lilly in North America. The development of vaccines to prevent the spread of common infectious diseases, the increased use of opiates (with the introduction of the hypodermic syringe), and the discovery of aspirin at the end of the nineteenth and early twentieth century resulted in cannabis-based medicines losing their prevalence in the market place and Western pharmacopoeia [2].

In Canada, the non-medical use of cannabis was outlawed as part of the Opium and Narcotics Drugs Act of 1923, largely based on a series of misleading articles written by Emily Murphy for *MacLean's Magazine* in the early 1920's which claimed cannabis turned people into raving, blood-thirsty lunatics [12]. The US Pharmacopoeia listed Cannabis until 1941 and stated that cannabis can be used for treating fatigue, coughing, rheumatism, asthma, delirium tremens, migraine headaches, and the cramps and depressions associated with menstruation [13,2].

Although modern research into therapeutic applications for cannabis has been seriously stymied by its prohibition in most of the Western world, extensive anecdotal reports and a growing body of laboratory and clinical research suggest that it may have many medicinal uses, including hunger stimulation for wasting syndrome; anti-emetic and anti-nausea properties in AIDS or cancer chemotherapy; anti-spasmodic properties for MS, epilepsy and other neurological dysfunctions; reducing intra-ocular eye pressure in glaucoma; and analgesic properties in a large number of chronic pain conditions [14-16]. Recent research has found that cannabis can reduce the use of pharmaceutical drugs and even be an effective treatment for addiction [17-20].

Medical Cannabis Access in Canada

Although the Canadian Addiction Survey suggests that about 1 million Canadians use cannabis for medical purposes [5], as of January 2010 the MMAD had only authorized 4884 people in Canada to use cannabis legally [21]. Additionally, the federal supply of cannabis produced by a company called Prairie Plant Systems since 2000 remains highly problematic due to a lack of strain selection, controversial production methods, and patient concerns over the quality and safety [3-5].

Problems of safe access were noted by the Canadian Senate Special Committee on Illegal Drugs in their final report on cannabis from 2002, stating that:

while a process that authorizes the possession and production of marijuana has been established in Canada, this has not ensured that cannabis is suitably available to those in need... we have come to the conclusion that the MMAR have become a barrier to access. Rather than providing a compassionate framework, the regulations unduly restrict the availability of cannabis to those who may receive health benefits from its use [22].

According to this report, one of the main reasons for the small number of applicants to the program is reluctance by physicians to act as gatekeepers to medicinal

cannabis. Citing a perceived lack of information on dosage, side effects, and alternate routes of administration to smoking, both the Canadian Medical Association and the Canadian Medical Protection Agency (which insures nearly 95% of Canada's physicians) have warned against the therapeutic use of cannabis, and have recommended that doctors not participate in the federal program. For example, a CMA press release dated July 9th, 2003, declares:

The CMA has consistently raised concerns about the lack of evidence-based decisions to support the Medical Marijuana Access Regulations," said Dr. Dana Hanson, President of the CMA. "Our unease over use of medical marijuana has been ignored in this new policy. Physicians should not be the gatekeeper for a substance for which we do not have adequate scientific proof of safety or efficacy [23].

Such warnings have been a particular deterrent for medical specialists, whose support was initially necessary for all applicants to the program that were neither terminally ill nor likely to die in the next 12 months, such as those suffering from MS, HIV/AIDS and hepatitis C (terminal patients only required the support of a single physician). In addition, specialists were simply not available in many smaller rural communities. When compounded by the bureaucratic hurdle of filling out a 29-page application that sometimes took in excess of 12 months for Health Canada to process, the challenges to participation in this program ranged from onerous to impossible for many potential applicants.

Health Canada officially amended the MMAD application process in 2005 to remove the requirement of a supportive specialist under most circumstances. However, the new "simplified" application form was now 33 pages long, and potential applicants continue to face resistance from the medical community. The burden of this difficult application process is apparent in comparing the MMAD with the state-run Oregon Medical Marijuana Program (OMMP), one of twelve state-administered medical cannabis programs in the U.S. Although both programs originated in 1999 and have similar medical requirements for registration, Oregon's simple two page application process has led to the registration of 23,873 participants as of October 2009 (as compared to just over 4000 in Canada during the same period) - despite having a population one-tenth that of Canada [24].

Community-Based Dispensaries

Community-based medical cannabis dispensaries, also called "compassion clubs", supply cannabis for therapeutic use upon a valid recommendation or confirmation of

diagnosis from a licensed healthcare practitioner, and reflect a patient-centered response to the suffering of critically and chronically ill Canadians who might benefit from the medical use of cannabis [3-5,7].

During the late 1980's, as rates of HIV and AIDS began to rise in San Francisco, a few underground dispensaries began offering a safe source of cannabis to those needing it for medical purposes were established by compassionate people living with HIV/AIDS and drug policy reform activists. With the successful passage in 1996 of a state ballot initiative called "Proposition 215", California became the first U.S. state to allow for the legal medical use and distribution of cannabis. Within a few weeks dozens of these "compassion clubs" opened, and although they often had varied policies and practices, their common goal was facilitating access to a safe supply of cannabis for medical users [25]. Since then, over 1000 community-based medical cannabis dispensaries have opened up in California [26], and it is estimated that they currently supply over 250,000 state authorized patients [27]. Similar organizations have emerged all over the world, and in Canada and the U.S. these dispensaries remain the main source of cannabis-based medicines for therapeutic use [3].

In Canada, a loose network of community-based dispensaries provide over 30,000 critically and chronically ill Canadians access to a safe supply of cannabis within an environment conducive to healing [8]. Although Canadian dispensaries continue to operate without legal sanction or protection, communities, law enforcement, and criminal courts across Canada have shown support and tolerance for compassion clubs that self-regulate to ensure their services are strictly for medical purposes [3-5]

Quality of Service Assessment of Health Canada's Medical Cannabis Policy and Program

Although Health Canada hosted a stakeholder consultation in 2003 to address some of the early constitutional and bureaucratic deficiencies of the MMAR, the opinion of patients registered with the MMAD has never been officially polled by the federal government in any systematic manner. This survey is an attempt to address the dearth of information about actual patient experiences with medical cannabis and Health Canada's program.

The study was funded by the McMaster Arts Research Council, and ethics approval was granted by the McMaster Research Ethics Board. Data gathering took place from April 2007 to Jan. 2008, eventually garnering survey responses from 100 federally-authorized users, which at the time represented about 5% of the patients enrolled in Health Canada's program. The 50 item self-administered survey combines multiple choice and

open-ended questions, and includes items informed by validated questionnaires like the Short-Form Patient Satisfaction Questionnaire (PSQ-18) and a 2005 questionnaire designed by Belle-Isle and the Canadian AIDS Society to identify barriers to medical cannabis experienced by Canadians affected by HIV/AIDS [5,6]. In addition to basic socio-demographic data, survey questions generated by the researcher to address the history of involvement and experiences with the federal program, cannabis use patterns, and specific symptoms and conditions that cannabis has relieved.

For privacy reasons Health Canada does not make a list of federally authorized medical cannabis patients available to the public, so recruiting for this study was conducted through online and hard mail outreach to medical cannabis patient internet discussion groups and community-based dispensaries. In order to ensure that survey participants were federally authorized patients, respondents were asked to type in a specific word only found on the authorized user ID card supplied by Health Canada as a password to access the online questionnaire. Although the identity of survey respondents will be kept completely anonymous, participants were also asked to supply the registration number from their Health Canada medical cannabis ID card to allow for future verification/authentication if necessary.

Demographic Data

Study participants were > 78% male and 20.4% female, and > 87% were 35 or older. Over 93% report that they are Caucasian, with 3 participants identifying as First Nations, 2 as Metis, and 1 as “black” (n = 97). In terms of income 36.8% make less than \$20,000, and > 61% make less than \$30,000, so this is a group that is well below the medium income in Canada, which may be the result of physical disabilities stemming from serious and/or chronic medical conditions. Although a medical expense income tax claim can be filed for the cost of cannabis purchased from the government, or produced by individuals or their designated grower, there is currently no reimbursement of the actual costs of medical cannabis. In light of these findings, it is unsurprising that 46.3% of respondents state that they can “never” afford enough cannabis to relieve their symptoms. Despite the low-income levels, 77.8 had graduated from high school, and 22.3% had a university degree (Table 1). According to Statistics Canada, this is slightly higher than the Canadian average; the 2006 Census found that just over 76% of Canadians had graduated from high school, and that 18% had a university degree equivalent to a Bachelor’s or higher [28].

Although there is no way to verify that this limited sample is representative of participants in the MMAD, a recent study by Reinerman et al assessing population

Table 1 Demographics of Federally Authorized, Medical Cannabis Patients

Female	20.4%
Male	78.6%
Caucasian	93%
Metis	2%
Black	1%
Other	4%
18-24	2%
25-34	10.2%
35-44	23.5%
45-54	39.8%
55-64	23.4%
65-74	1%
Elementary School	5.1%
Secondary School	21.2%
Technical and Non-University Education	33.3%
University (Undergrad, BA)	18.2%
University (MA, PhD, post-doc)	5.1%
Less than \$10 000	8.2%
\$10 000-19 999	28.6%
\$20 000-29 000	24.5%
\$30 000-39 000	11.2%
\$40 000-49 000	5.1%
\$50 000-59 000	12.2%
\$60 000 and over	10.2%

characteristics of 1746 California-based medical cannabis patients offers some useful comparisons. Reinerman et al found that 72.9% of their sample was male, with the researchers theorizing that the underrepresentation of women may be related to the gender-distribution of certain kinds of sports or workplace injuries, as well as the “...double stigma women face in seeking MM (medical marijuana) - for using an illicit drug and for violating gender-specific norms against illegal behavior in general” [19].

Additionally, Reinerman et al found this population to be of slightly higher education levels than the general population, with 93.1% reporting at least high school graduation, and 23.8% having a post-secondary degree, which is also similar to this Canadian survey.

Patient Use Patterns and Preferences

While the overwhelming majority of participants reported using cannabis recreationally prior to their medical use, > 20% were cannabis-naïve prior to using it medically (n = 89). The average years of medical use is just over 10 years, which may be reflective of the older patient profile and additionally suggests that many patients have been using cannabis for far longer than Health Canada’s federal program has been in existence. When asked to check off all the major symptoms for

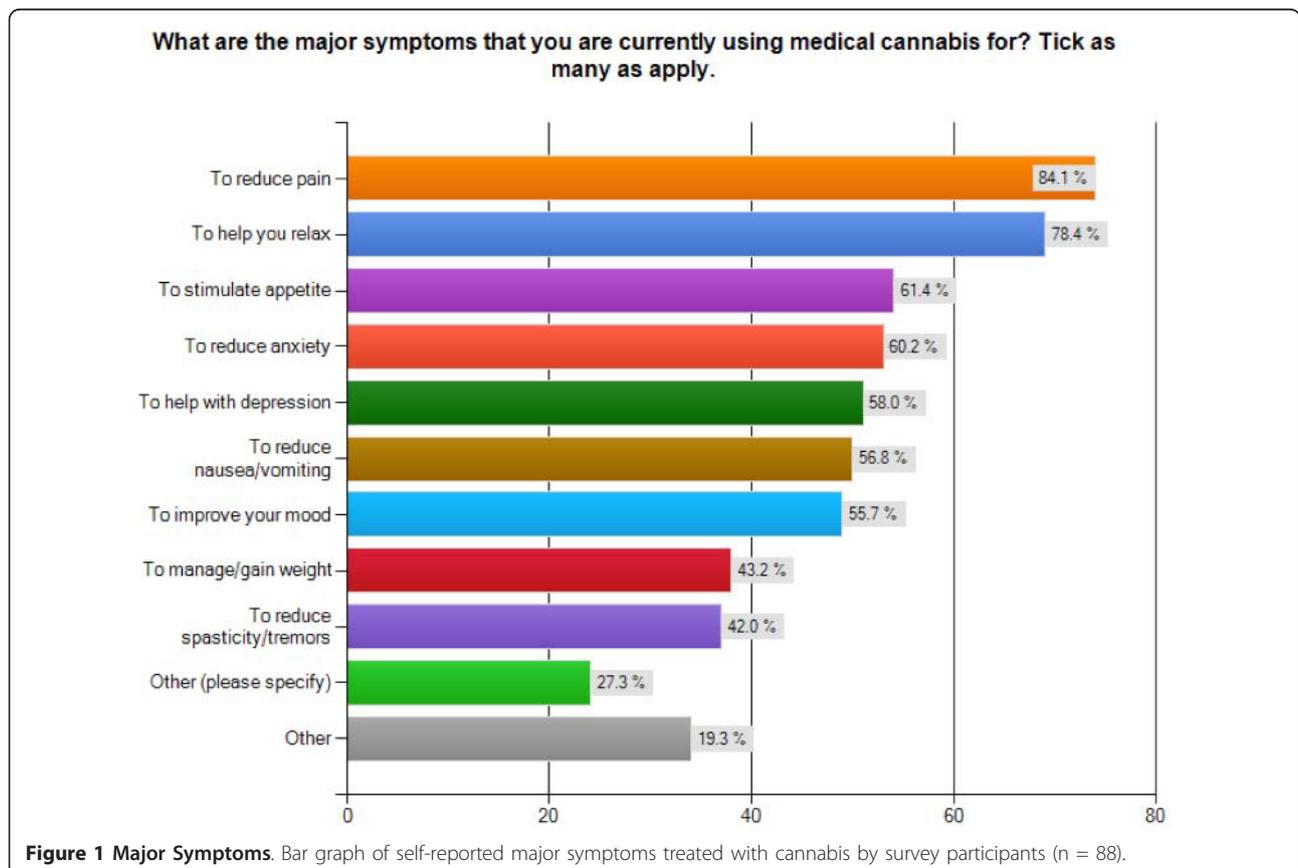
which they used medical cannabis, most cited multiple symptoms: 84.1% cited pain relief, 78.4% cited relaxation, 61.4% cited appetite stimulation, 60.2% cited anxiety reduction, 58% cited depression, 56.8% cited nausea reduction/vomiting, 55.7% cited mood improvement, 43.2% cited desire to manage/gain weight, 42% cited reduction in spasticity/tremors, and 23.9% cited side-effects of other medications. Of interest is the high number of individuals using cannabis for relaxation, anxiety reduction, depression and mood improvement, suggesting that patients with physical health conditions may also be self-medicating for mental health issues and/or general improvements in their quality of life (Figure 1).

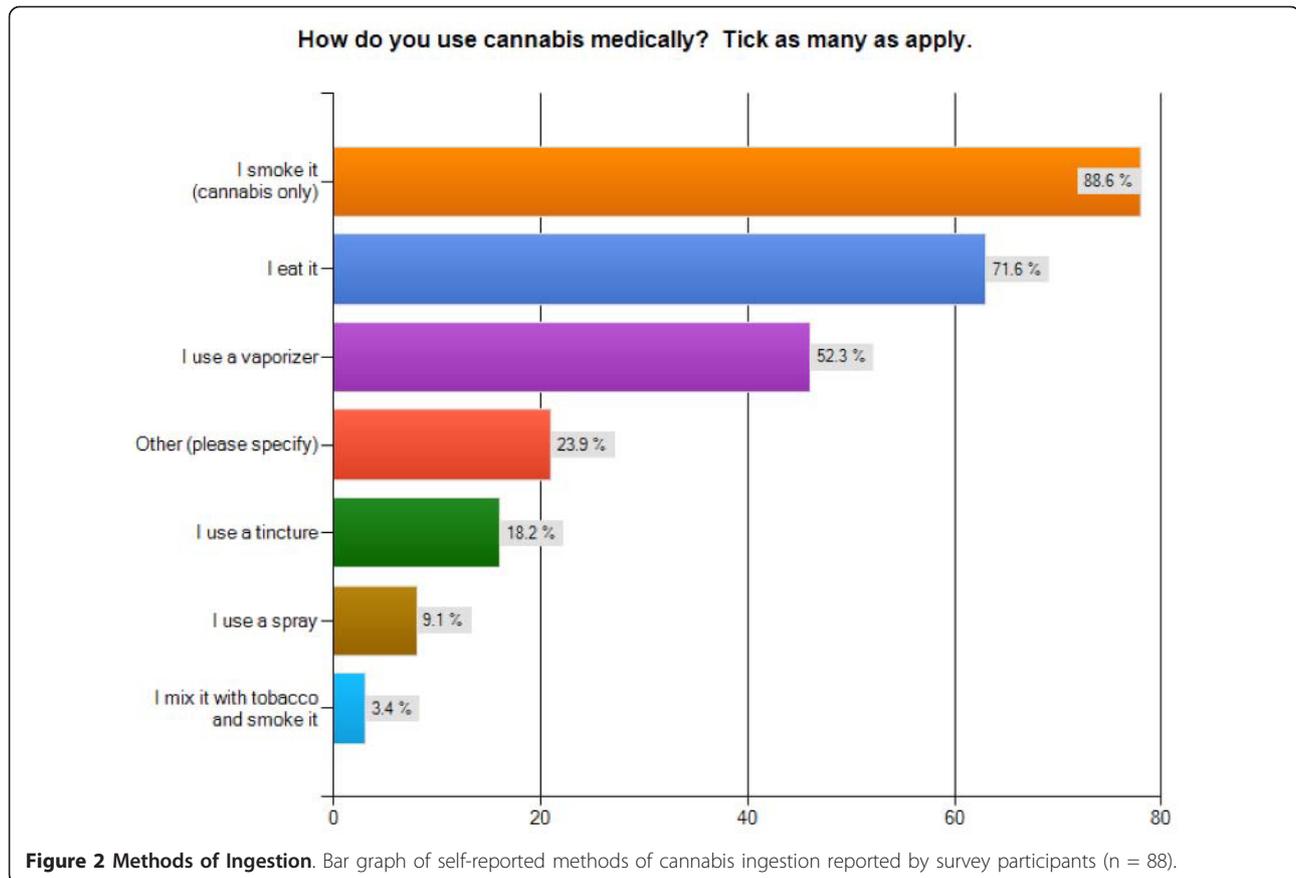
In terms of personal use patterns, over 94% stated that they use it every day, which is considerably higher than the 67% reported by Reinarman et al from their California patient survey [19]. Over 88% smoke cannabis, and 71.6% report that they eat it. Over 52% have used vaporizers, 18.2% use tinctures and, unlike Europe, less than 4% mix it with tobacco. While the rate of smoking is similar to the Reinarman et al sample, which found that 86.1% smoke cannabis [19], the comparatively higher use oral ingestion/edibles (71.6% v. 24.4%) and vaporizers (52% v. 21.8%) in the Canadian sample may suggest

a greater level of concern and mitigation for potential health impacts associated with smoking within the Canadian patient population [29] (Figure 2). This health awareness may also explain why 80.7% of respondents prefer to use cannabis grown using certified organic cultivation methods, whereas 19.3% either don't care (14.5%) or prefer non-organic cultivation (4.8%).

In terms of patient preferences and treatment efficacy, 90.9% report that not all strains are equally effective at relieving their symptoms. As a result, 97.6% would prefer to obtain cannabis from a source that offers a "large selection of different strains" rather than 1 or 2 strains, and over 90% would prefer to have access to raw cannabis as well as other methods of ingestion like baked goods, tinctures, and hashish, compared with 9.8% who would prefer a cannabis-only outlet. This creates a stark contrast between access through Health Canada and through community-based dispensaries. While Health Canada offers a single strain of raw cannabis and no alternatives to smoking, dispensaries make multiple strains and methods of ingestion other than smoking available to patients, including edibles, oils, tinctures, salves, and even oromucosal sprays [3].

When asked about other cannabinoid-based pharmaceutical medicines like Marinol (dronabinol), Cesamet





(nabilone) and Sativex, 34.9% had tried Cesamet, 33.7% had tried Marinol, and 14% had tried Sativex. 43% had not tried any of the above, and 81.5% stated that didn't use any of these pharmaceuticals on a regular basis.

Patient Access to Medical Cannabis

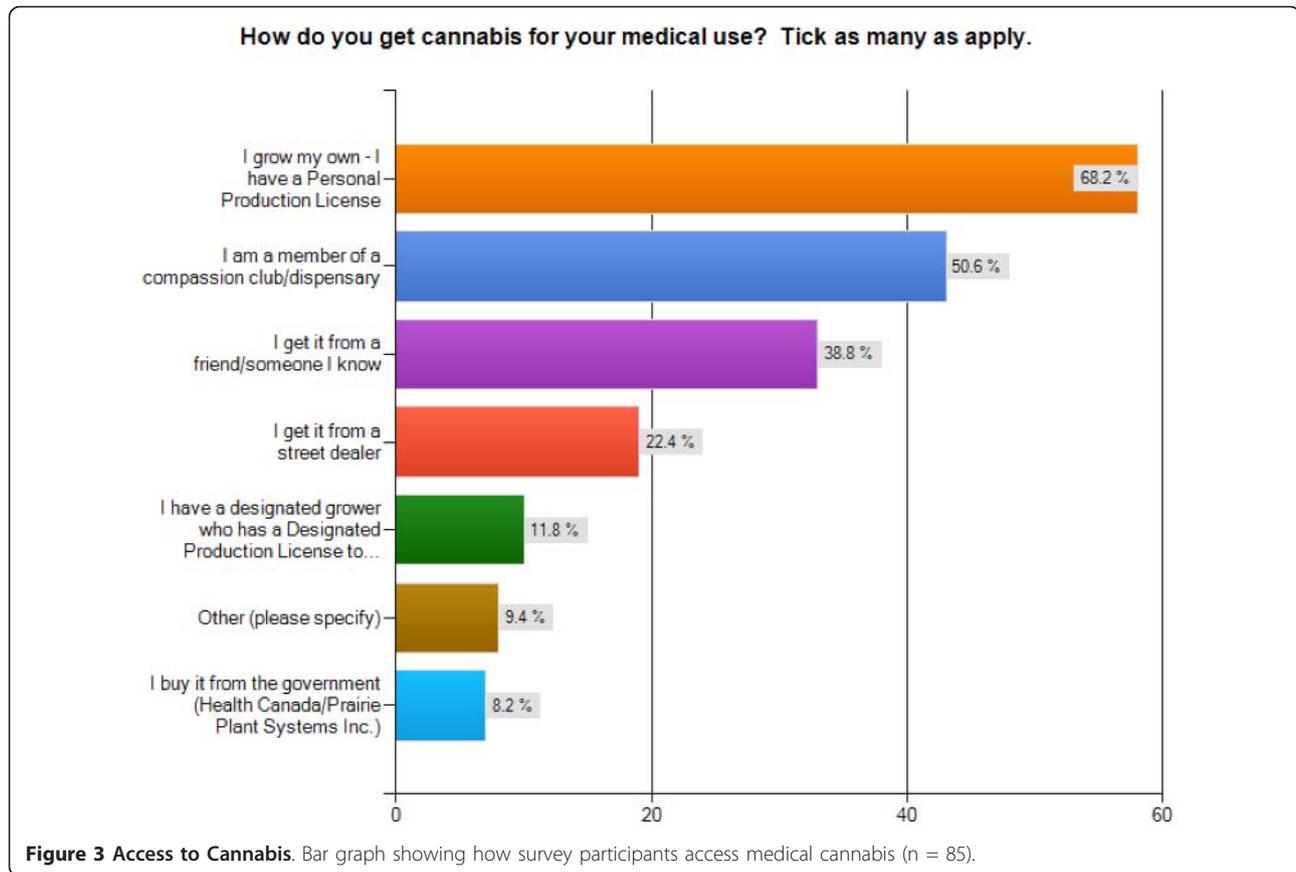
When asked how they obtain cannabis, only 8.2% of respondents report getting their cannabis from Health Canada (although nearly half state that they have tried the federal supply), while 80% grow it for themselves or have it grown for them by a Designated Producer. Over 50% report that they frequent compassion clubs or dispensaries, 38.8% report getting it from a friend, and > 22% get their medicine from street dealers (Figure 3).

When asked how they would rank the quality of the cannabis from their regular source, 87.8% rank it as 7 or above in a scale of 1-10, with 1 being "Very Poor", and 10 being "Excellent". By comparison, of the 41 patients who have tried the federal cannabis supply, over 75% rank it as either 1 or 2 on a scale of 1-10. While 3 respondents ranked it as either a 6, 7, or 8, no one ranked it any higher (Figure 4).

Since Health Canada's cannabis supply went through some modest improvements in regards to the size of the grind, humidity level, and amount of THC in August

2004, respondents were asked when they tried this cannabis. Of the 39 who answered this question, 37 (or > 94%) used the federal supply between 2005-2007, and 2 used it before that. As such, it can be deduced that the general dissatisfaction with the quality of the federal cannabis supply is based on patient experiences with the most recent "improved" version of this product.

When asked what their single preferred source for medical cannabis would be, 65.1% stated that they would like to grow their own, 24.1% cited dispensaries, 6% would like to get their medicine from a pharmacy, 4.8% would like to get it from a friend, while neither street dealers nor Health Canada were cited by a single patient as their preferred source. This is highly relevant since Health Canada's proposed regulatory changes include removing the right for individuals to produce their own cannabis, despite this being the preferred option cited by most study participants and the option chosen by the majority of patients in the federal program [30]. As of January 2010 (the latest statistics available on the Health Canada website) 3576 out of 4884 - or over 73% - of federally authorized patients chose to produce their own medicine or to have a Designated Producer do so for them [21]. If Health Canada intends to make this program more patient-centered, removing



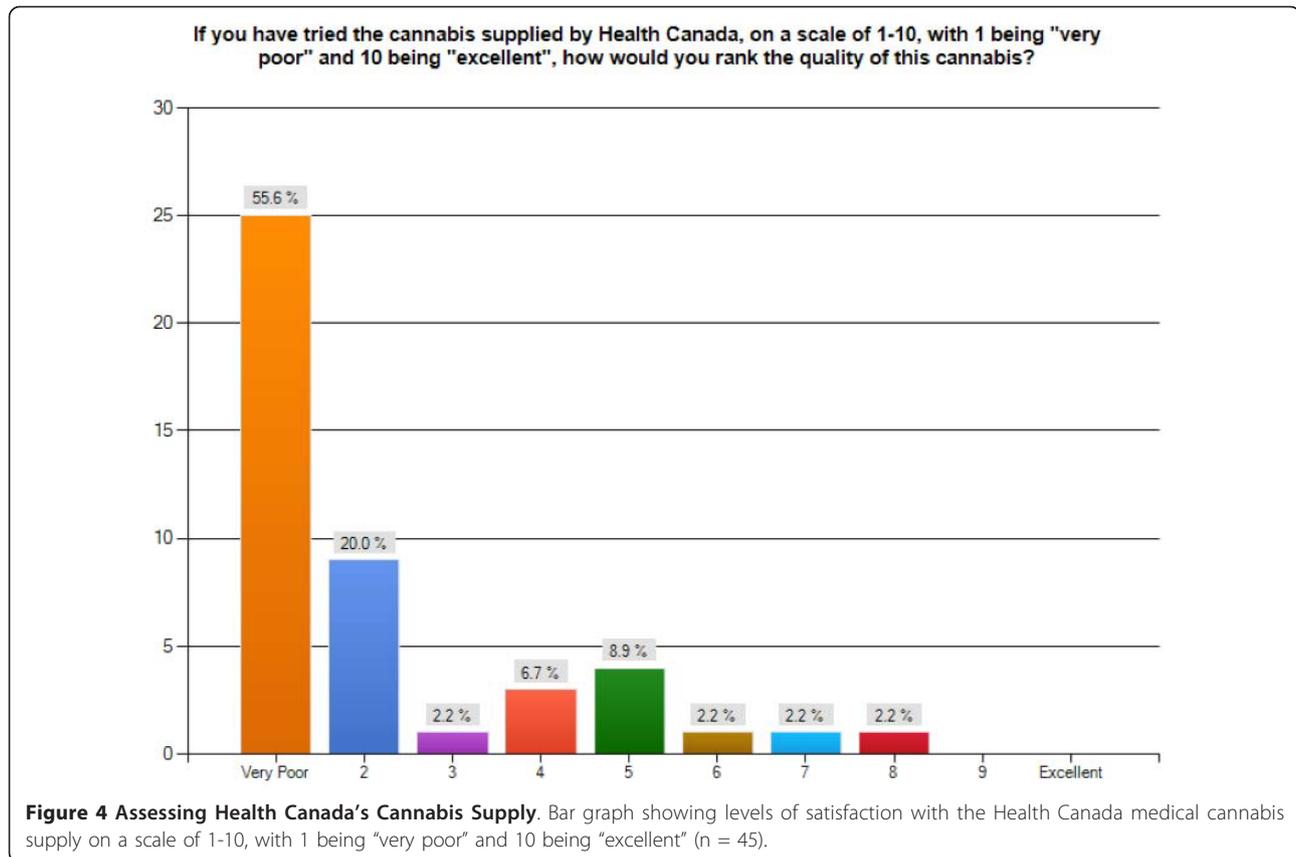
the right for patients to produce their own supply does not appear to reflect current patient needs, and as such this proposed significant amendment to the program should be highly controversial, and will likely lead to further court challenges by patients wishing to control the cost and quality of their supply of medicine.

Patient Experiences With Health Canada Marijuana Medical Access Division

Of study participants, nearly half (49.3%) became federally authorized patients in 2004 or later, while 50.7% joined the program prior to 2004. When asked if they had difficulty finding a physician to support their application, exactly 50% said “yes”, and 50% answered “no”, reflecting the diversity and unpredictability of medical support available throughout Canada. In terms of processing applications, 35.3% had theirs completed by Health Canada within 2-4 months, and 29.4% state that it took 60 days or less. However, 35.2% of participants suggest that it took over 4 months, with 17.6% citing that they waited over 12 months for their application to be processed. This suggests that for those suffering from serious or terminal conditions, processing times would be a significant concern and may not be quick enough

to allow some patients to legally use cannabis in end-of-life situations.

The following set of 6 questions put three statements with positive connotations and 3 statements with negative connotations to survey respondents, and are based on standardized and validated Short-Form Patient Satisfaction Questionnaire (PSQ-18) traditionally used to evaluate health service delivery at hospitals, clinical and insurance companies. In addressing the statement “I find the application for a federal authorization simple and uncomplicated”, only 21.8% “agreed” or “strongly agreed”, while 71.2% “disagreed” or “strongly disagreed” (42.5%), suggesting that for most patients the federal application process is onerous and challenging. When asked to comment on the statement “Employees at Health Canada’s MMAD act too businesslike and impersonal towards me”, 54% “agreed” or “strongly agreed”, while 28.7% “disagreed” or “strongly disagreed”. In regards to the statement “I am dissatisfied with the service I receive from Health Canada in regards to my use of medical cannabis”, 68.9% “agree” or “strongly agree”, while only 18.3% “disagree” or “strongly disagree”. However, when asked if “Employees at Health Canada’s MMAD treat me in a friendly and courteous manner”, respondents were split, with 35.6% “agreeing” or “strongly



agreeing", 27.6% "uncertain", and 36.8% "disagreeing" or "strongly disagreeing". When the statement "I have full confidence in the ability of the Health Canada employees that administer this program" was put to patients, 76.8% "disagreed" or "strongly disagreed", with only 5.9% "agreeing" or "strongly agreeing" with the statement, and 17.4% stating that they were "uncertain". Finally, when asked "I am able to get help from Health Canada in regards to my medical use of cannabis whenever I need it", 8.2% "agreed" or "strongly agreed", while 70.6% "disagreed" or "strongly disagreed", with 21.2% uncertain.

The final question of the survey asked participants to rate their overall satisfaction with Health Canada's medical cannabis program, and 15.1% of patients state that they are "completely" or "somewhat satisfied", 12.8% uncertain, and 72.1% either "somewhat" (20.9%) or "totally unsatisfied" (51.2%) (Figure 5). This suggests a very poor patient perception of the service quality at Health Canada Marihuana Medical Access Division, with many potential improvements in application processing times, cannabis selection and quality and overall responsiveness to patient queries and concerns.

In a federally-funded report titled "Our Rights, Our Choice," which examined the human rights, ethical and legal challenges faced by people living with HIV/AIDS

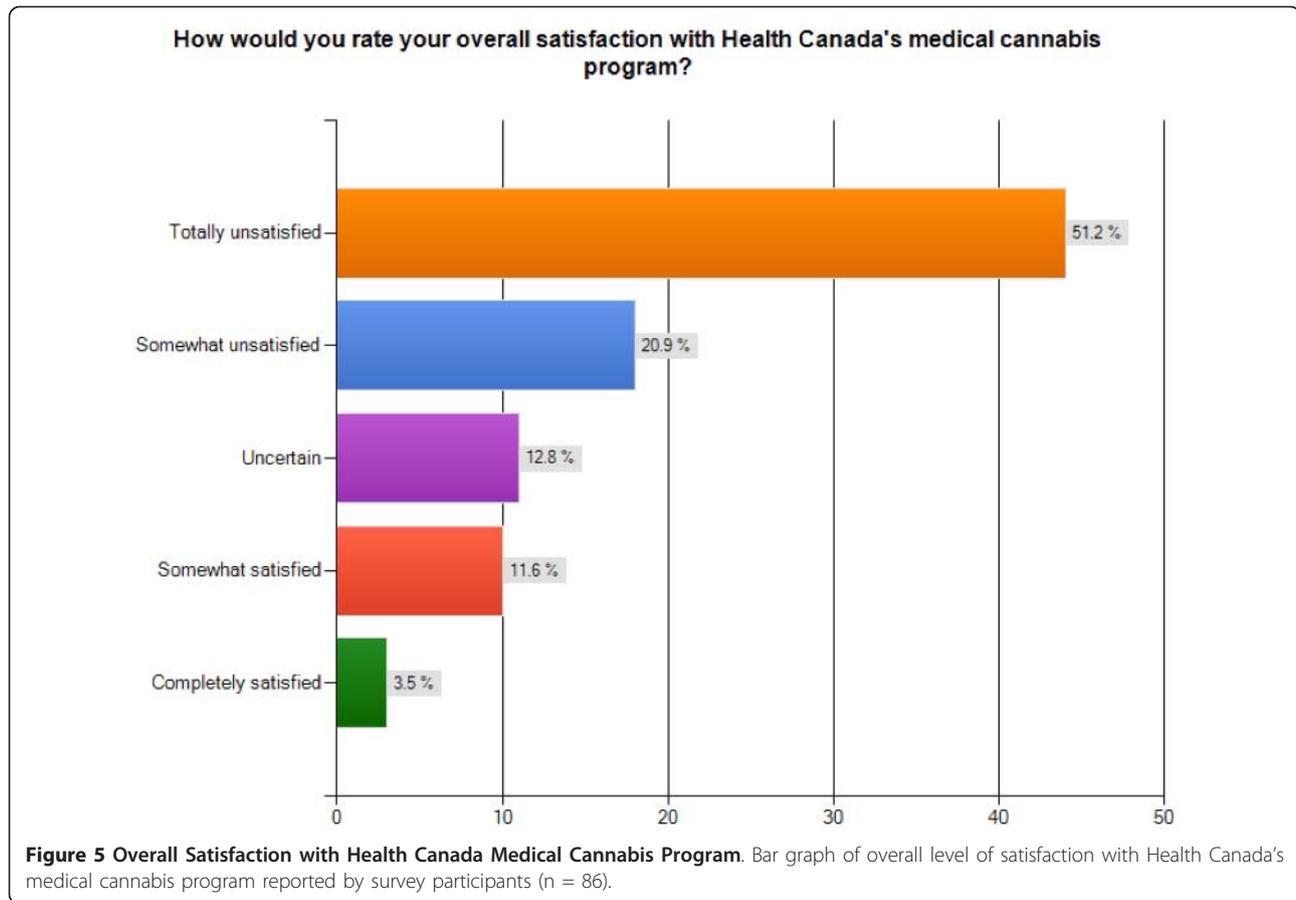
who choose to use medical cannabis, the Canadian AIDS Society found that although between 14 to 37% of people living with HIV/AIDS used cannabis to address their condition, many had faced hurdles accessing the federal program. The CAS report states that:

access to the federal program remains hindered by barriers such as a lack of awareness of the program's existence, mistrust in the government, misinformation about the program and difficulty in finding a physician to support their application. Thousands of seriously ill Canadians must therefore choose between breaking the law to use the therapy of their choice, or going without, which in many cases compromises their well-being and quality of life [6].

The results of this federally authorized medical cannabis patient survey support the findings of the CAS study and other research into the MMAR/MMAD [3-5].

Discussion

Creating policies and procedures for safe patient access to medical cannabis has proven to be a challenge in Canada and around the world. In the U.S., the 14 states that allow for the legal use of cannabis continue to



struggle to protect patients, address access issues, and mitigate community concerns, all of which is made all the more complicated by ongoing resistance and active legal threats by the federal government [7]. In Canada, patients face multiple challenges to safe access: 1) resistance from the medical community to act as gatekeepers to the program; 2) an onerous application process; 3) a very limited and much-criticized cannabis supply; 4) limited income and a lack of national cost-coverage; and 5) ongoing social prejudice against the use of medical cannabis [3-6]. Results from this survey suggest that reducing bureaucratic obstacles while increasing patient options for access would result in greater levels of patient participation and overall satisfaction with the federal program.

While there is a remarkable diversity in the demographics and medical conditions of cannabis patients, some common themes emerge from this research. It is clear that patients' would like to have a choice of many different strains and forms of ingestion in order to more safely and effectively address their many different symptoms and conditions. Since cost continues to be a significant obstacle for patients with low or fixed income, provincial or federal cost-reduction or coverage policies

should be implemented [5,6]. The high bureaucratic burden on both patients and physicians is reducing participation in the program, so allowing healthcare providers to treat cannabis like any other medicine would likely improve uptake and might also alleviate some of the social stigma associated with the therapeutic use of cannabis. Since this study and Health Canada's own statistics [21] show that the majority of participants in the Canadian federal program chose to produce their own medicine, policies and procedures should be put in place that maintain the option of personal production while also ensuring that both patients and communities are protected from the dangers of poorly-cultivated cannabis. This could range from basic information from Health Canada on safe production practices to electrical inspections at the municipal level. Additionally, with over half of respondents currently accessing cannabis through dispensaries and growing evidence that these organizations build social capital and provide an environment that is conducive to health and healing [3-7], the federal government should work with dispensaries to develop regulations that would incorporate this community-based model of access into Canada's medical cannabis program.

Finally, many of the challenges faced by the MMAD could have been addressed or avoided through a more robust and active strategy for patient engagement and involvement. Although there are many stakeholders directly or indirectly affected by the federal medical cannabis program - municipalities, police, physicians, etc. - the key stakeholders are the Canada's critically or chronically ill who could or do benefit from the use of cannabis. Unfortunately, the short history of the MMAR/MMAD shows that the needs and concerns of patients has all too often been ignored or overshadowed by other interests and concerns [3-6]. The future success of this cutting-edge program will depend largely on the willingness of the federal government to create a truly patient-centered approach to medical cannabis access, including active and ongoing engagement with end-users, support for research into the potential harms and benefits of medical cannabis, and increased options for patients, potentially through the regulation of community-based dispensaries.

There are a few limitations to this study. Although participants represented about 5% of the patient population in the program at the time of the survey there is no way to know how representational this cohort is to the rest of the participants in the MMAD since Health Canada has never released any demographic information about federally authorized users. Additionally, since recruiting was largely done online and through medical cannabis patient lists and groups, it is possible that this more active population has a higher level of dissatisfaction with the federal program. However, the general demographics of participants in this study is similar to those identified by Reinerman in a recent U.S.-based study [19], and many of the patient needs and challenges that came to light in this survey support previous research on Canada's medical cannabis population and associated federal program [3-6]. It is hoped that this survey, which represents the first polling ever conducted solely on federally authorized patients in Canada, will assist policy-makers here and abroad develop more patient-centered strategies for safe access to medical cannabis.

Acknowledgements

The author would like to gratefully acknowledge all of the federally authorized medical cannabis patients who took time to share their experiences by participating in this survey. Additionally, I'd like to thank the McMaster Arts Research Council for funding this study, Andy Hathaway PhD for coordinating the interview component of this research project, and Lynne Belle-Isle PhD Candidate for translating the questionnaire into French.

Competing interests

Philippe Lucas is the founder of the Vancouver Island Compassion Society (VICS), and was employed as Executive Director of during the design and data gathering portions of this study. While he is no longer an employee of the VICS, he remains a member of the board.

Received: 26 August 2011 Accepted: 3 January 2012
Published: 3 January 2012

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doi:10.1186/1477-7517-9-2

Cite this article as: Lucas: 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* 2012 **9**:2.

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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

Published: 04 October 2005

Received: 17 August 2005

Harm Reduction Journal 2005, **2**:18 doi:10.1186/1477-7517-2-18

Accepted: 04 October 2005

This article is available from: <http://www.harmreductionjournal.com/content/2/1/18>

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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.

Acknowledgements

Thanks to all the participants for sharing their experiences and to: Andrew Kavasilas for permission to adapt his questionnaire and ongoing support; and Graham Irvine, Franjo Grotenhermen, Laurie Mather, Wayne Hall and Louisa Degenhardt for comments on the questionnaire.

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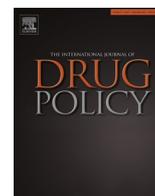
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Research paper

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

ARTICLE INFO

Article history:

Received 27 September 2016

Received in revised form 15 December 2016

Accepted 10 January 2017

Available online xxx

Keywords:

Cannabis

Marijuana

Opioids

Substitution

Pain

Mental health

Addiction

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-

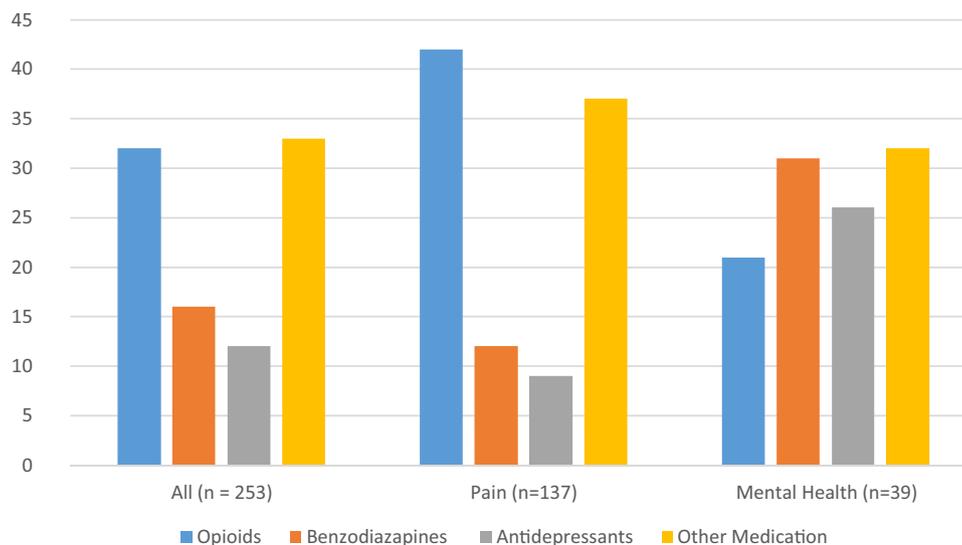


Fig. 1. Substitution by condition.

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.

Acknowledgements

Funding for this study was provided by Tilray. We would like to thank all of the Tilray patients that have shared their thoughts and experiences with us, as well as Kim Crosby for assisting with some of the data analysis of this survey.

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Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors

PHILIPPE LUCAS¹, ZACH WALSH², KIM CROSBY³, ROBERT CALLAWAY⁴,
LYNNE BELLE-ISLE^{1,5}, ROBERT KAY⁶, RIELLE CAPLER⁷ & SUSAN HOLTZMAN⁸

¹Centre for Addictions Research of British Columbia, University of Victoria, Victoria, Canada, ²Psychology, The University of British Columbia, Kelowna, Canada, ³Psychology, The University of British Columbia, Kelowna, Canada, ⁴Medical Cannabis Advocate, Vancouver, British Columbia, Canada, ⁵Canadian AIDS Society, Ottawa, Canada, ⁶GreenLeaf Technologies, Kelowna, British Columbia, Canada, ⁷Interdisciplinary Studies Graduate Program, University of British Columbia, Vancouver, Canada, and ⁸Department of Psychology, University of British Columbia, Kelowna, Canada

Abstract

Introduction and Aims. Recent years have witnessed increased attention to how cannabis use impacts the use of other psychoactive substances. The present study examines the use of cannabis as a substitute for alcohol, illicit substances and prescription drugs among 473 adults who use cannabis for therapeutic purposes. **Design and Methods.** The Cannabis Access for Medical Purposes Survey is a 414-question cross-sectional survey that was available to Canadian medical cannabis patients online and by hard copy in 2011 and 2012 to gather information on patient demographics, medical conditions and symptoms, patterns of medical cannabis use, cannabis substitution and barriers to access to medical cannabis. **Results.** Substituting cannabis for one or more of alcohol, illicit drugs or prescription drugs was reported by 87% ($n = 410$) of respondents, with 80.3% reporting substitution for prescription drugs, 51.7% for alcohol, and 32.6% for illicit substances. Respondents who reported substituting cannabis for prescription drugs were more likely to report difficulty affording sufficient quantities of cannabis, and patients under 40 years of age were more likely to substitute cannabis for all three classes of substance than older patients. **Discussion and Conclusions.** The finding that cannabis was substituted for all three classes of substances suggests that the medical use of cannabis may play a harm reduction role in the context of use of these substances, and may have implications for abstinence-based substance use treatment approaches. Further research should seek to differentiate between biomedical substitution for prescription pharmaceuticals and psychoactive drug substitution, and to elucidate the mechanisms behind both. [Lucas P, Walsh Z, Crosby K, Callaway R, Belle-Isle L, Kay B, Capler R, Holtzman S. Substituting cannabis for prescription drugs, alcohol, and other substances among medical cannabis patients: The impact of contextual factors. *Drug Alcohol Rev* 2016;35:326–333]

Key words: cannabis, marijuana, substitution effect, substance use, addiction.

Introduction

The medical use of cannabis can be traced back at least 5000 years [1,2], and by the late 19th century, cannabis-based preparations were widely marketed for medical use [3]. A variety of social and technological developments led to the stigmatisation and marginalisation of cannabis by the 1920s [4,5], and by

the 1940s, the international implementation of cannabis prohibition put an end to nearly all research into the use of cannabis for therapeutic purposes (CTP). The past decade has witnessed an increased interest in the therapeutic properties of cannabis, and a growing body of laboratory and clinical research attests to the many uses of cannabis-based medicines for diverse symptoms and conditions [6–9].

Philippe Lucas MA, PhD, Student, Social Dimensions of Health, University of Victoria, VP, Patient Research and Services, Zach Walsh PhD, Associate Professor, Kim Crosby MA, Robert Callaway MA, Medical Cannabis Advocate, Vancouver, British Columbia, Canada, Lynne Belle-Isle PhD, Social Dimensions of Health, University of Victoria, Candidate, Robert Kay GreenLeaf Technologies, Kelowna, British Columbia, Canada, Rielle Capler MHA, PhD, Student, Susan Holtzman PhD. Correspondence to Mr Philippe Lucas, University of Victoria, Social Dimensions of Health, 3800 Finnerty Rd, Victoria, British Columbia, Canada; V8P 5C2, Tilray, 1100 Maughan Rd., Nanaimo, British Columbia, V9X1J2, Canada. Tel: 250-588-1160; Fax: 1-888-783-1323; E-mail: plucas@uvic.ca

Received 11 November 2014; accepted for publication 6 July 2015.

Concurrent with increased recognition of the legitimate therapeutic use of cannabis is an international reappraisal of prohibitions for extra-medical cannabis use, with several nations exploring the potential costs and benefits of establishing legal access to cannabis outside of the medical system [10]. Legal access to cannabis might affect the broader social costs related to the use of both licit and illicit psychoactive substances, and a comprehensive analysis of the consequences of cannabis use must recognise potential effects on the use of other psychoactive substances such as prescription drugs, alcohol and illicit substances.

Substitution effect

Substitution of psychoactive substances can be conceptualised within the context of behavioural economics, whereby commodities may have substitution, complementary or independent interrelationships with regard to rates of human consumption. In a seminal investigation of substitution and addictions, Hursh and colleagues [11] noted several factors that may affect substitution of one psychoactive substance for another, including changes in policy that affect availability, and changes to legal risk and associated repercussions. Population-level studies have identified substitution resulting from shifts in the legal risk associated with the use of a particular substance, such as decriminalisation [12].

In regards to psychoactive/pharmacological substitution, Hursh *et al.* [11] add that ‘pharmacological therapies for the treatment of drug abuse can also be conceptualised as alternative commodities that either substitute for illicit drug use (e.g. agonist therapy) or reduce the potency of illicit drugs directly (e.g. narcotic antagonist therapy)’ (p. 25). Prominent examples of the harm-reducing potential of substituting one psychoactive substance for another include the prescription use of methadone as a substitute to injection heroin use [13] and the use of nicotine patches to curb or stop tobacco smoking [14]. Additionally, the cannabis extract nabiximols [Sativex (<http://www.gwpharm.com/Sativex.aspx>)] has been investigated as a potential agonist for cannabis withdrawal in a treatment-seeking cohort, finding that while nabiximols attenuated cannabis, which is a 1:1 THC/CBD buccal spray, withdrawal symptoms, placebo was as effective in promoting long-term reductions in use [15].

The use of cannabis as a substitute for prescription drugs, alcohol and other substances has been identified in a number of studies. Deliberate cannabis substitution has been reported by heroin and pharmaceutical opiate users [16]. A number of smaller studies have also found that cannabis appears to reduce the cravings for other drugs of dependence like crack cocaine [17], alcohol

[18] and opiates [19–21], and may improve some treatment outcomes for substance dependence [22]. A complementary line of research has found that cessation of cannabis use is associated with increased use of other substances like alcohol and cigarettes [15,23].

The effectiveness of cannabis as a substitute for other substances has been proposed to reflect diverse neurochemical and cognitive processes [17]. From a patient perspective, recent surveys of CTP users in Canada and the USA identified less withdrawal, fewer side effects, and better symptom management as primary reasons for cannabis substitution [6,18,24].

Medical cannabis in Canada

In Canada, several court cases have upheld the rights of patients to choose cannabis as medicine (e.g. *R. v. Smith, 2013*; *R. v. Beren and Swallow, 2009*; *Hitzig et al. v. Canada, 2003*; *R. v. Parker, 2000*; *Wakeford v. Canada, 2000*), and the 2001 *Marihuana Medical Access Regulations* established means for Canadians to obtain legal authorisation to possess CTP. Despite widespread concern with the efficiency of the Health Canada programme [25–28], registration has grown from fewer than 500 registrants in 2002 to over 26 000 in 2012 [29]. However, the *Marihuana Medical Access Regulations* have been noted for presenting substantial barriers to access [25–28], and fewer than 10% of the estimated one million Canadian individuals who use CTP are authorised through the federal programme [28,30,31]. The authorised versus unauthorised status of users of CTP represents a legal risk factor that might be expected to influence substitution.

Ability to afford CTP has also been identified as an important factor that affects access [25,31], and may therefore be expected to impact substitution. Additionally, several studies have identified analgesia as a prominent reason for using CTP, and cannabis has several potential advantages relative to widely used opiate analgesics including fewer side-effects, a lower risk of dependence, and no possibility of fatal overdose [20]. Therefore, those who use cannabis to address pain-related conditions might be expected to report relatively higher rates of substitution for prescription drugs for pain. History of problematic substance use might also influence rates of substitution, as individuals working to maintain abstinence from other substances may be more likely to use cannabis as a substitute [19].

In sum, prior research has identified cannabis as a potential substitute for other substances among CTP and community samples, however no studies have examined the extent to which cannabis substitution varies according to theoretically important factors such as authorisation to possess cannabis, affordability

of cannabis, substance use history, medical condition, and age. We expect that higher levels of access associated with authorised status and with greater affordability of CTP will be associated with increased likelihood of cannabis substitution for prescription drugs, alcohol, and illicit drugs, and that younger patients will be more likely to report substitution effect for alcohol and illicit substances due to the higher rates of use of these substances in those under 40 years old in the general population. Finally, we predict that individuals with histories of problematic substance use will report higher rates of substitution for alcohol and illicit substances.

Methods

Participants were 473 self-identified current users of CTP drawn from the Cannabis Access for Medical Purposes Survey (CAMPS) [32], with complete data regarding use of cannabis as a substitute. CAMPS is the largest polling of Canadian medical cannabis patients to date, and involved the administration of multi-part questionnaire of 414 forced choice and open-ended items that queried demographic information, medical conditions and symptoms, and patterns of cannabis use. Participants were surveyed in 2011–2012 online or in person at a medical cannabis dispensary. The study and survey were developed with the assistance of a community research board, and recruitment was assisted by dispensaries, by organisations that serve people who use CTP (e.g. Canadian AIDS Society, Canadian Aboriginal AIDS Network), and by social media and traditional media reporting on the project. The study was reviewed and approved by the Behavioural Research Ethics Board of the University of British Columbia. Respondents were 68% men, 90% European-Canadian and 9% Aboriginal. Ages ranged from 17 to 78 years, with a median age of 40. Participants presented with the range of conditions that is generally consistent with surveys of CTP users, the most prominent conditions being pain (32%), mood (i.e. anxiety and depression; 18%), arthritis (15%), HIV (10%), gastrointestinal disorder (7%) (Table 1; see Walsh *et al.*, 2013 [32] for a detailed account of CAMPS methodology and participant characteristics).

Substitution was measured using three dichotomous items (yes/no), each of which referred to a distinct class of substance. Participants were asked if they had substituted cannabis for: (i) prescription drugs; (ii) alcohol; and (iii) illicit substances. Positive responses branched to a follow-up query asking participants to rank six reasons for substitution as follows: *less adverse side effects from cannabis, less withdrawal symptoms with cannabis, the ability to obtain cannabis versus other drugs, social acceptance of cannabis is greater than other drug, better symptom*

Table 1. Sample characteristics

	CTP users, % (n)
Gender	
Male	68 (319)
Ethnicity	
European-Canadian	90 (424)
Aboriginal	9 (41)
Medical condition	
Pain	32 (149)
Mood	18 (81)
Arthritis	15 (71)
HIV/AIDS	10 (45)
GI	7 (32)
Age (years)	
18–24	15 (68)
25–34	25 (114)
35–44	20 (90)
45–54	26 (115)
55+	14 (63)
Education	
<HS	4 (18)
HS grad	38 (180)
Post secondary	58 (275)
Income (\$)	
<20 000	33 (160)
20 000–39 999	25 (118)
40 000–59 999	17 (78)
60 000+	24 (111)
Residence	
Rural	21 (97)
Urban	79 (370)

CTP, cannabis for therapeutic purposes; GI, gastrointestinal disorder; HS, high school.

management from cannabis than from alcohol or other drugs, and an *other* category, which was followed by space for an open response. This approach and the selection of items for the substitution reasons are derived from prior studies of substitution [6,18].

Participants were asked to indicate the single primary *condition* treated with cannabis, as well as any number of primary symptoms cannabis use alleviated (Figure 1). We created a dichotomous *pain condition* variable by aggregating respondents who identified the primary condition treated with CTP as spinal pain, non-spinal pain, or arthritis ($n = 220$), and comparing these participants to an aggregation of all other conditions ($n = 241$). A large contingent of these non-pain respondents nonetheless endorsed *pain* among the symptoms for which they used CTP (71%, $n = 171$), therefore, we conducted supplementary analyses comparing those who endorsed treating pain with CTP among a list of symptoms (83%, $n = 390$) with those who did not endorse treating pain with CTP (17%, $n = 82$). We also compared those who used cannabis primarily to treat the *depression* or *anxiety* ($n = 81$) to an

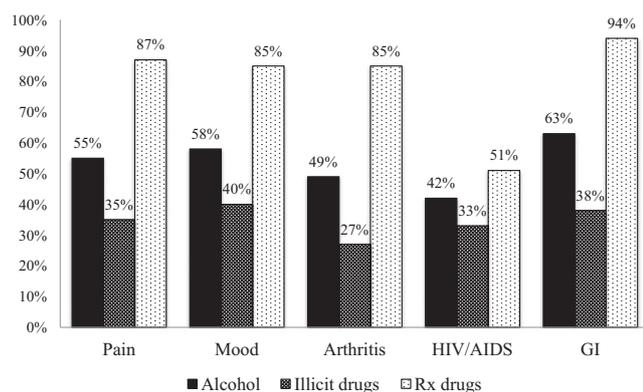


Figure 1. Frequency of substitution across top five reported medical conditions.

aggregation of all other conditions ($n = 379$). Approximately, one-third of respondents had obtained federal authorisation to possess cannabis (32%, $n = 152$), and we used a dichotomous *authorisation* variable to compare authorised versus unauthorised patients. Participants were queried regarding ability to afford CTP, and were divided into those who could *always* or *often* afford CTP (46%, $n = 214$) and those who could *sometimes* or *never* afford CTP (54%, $n = 252$). We also compared respondents with a history of treatment for problematic alcohol or other substance use (15%, $n = 71$) to those with no such history (85%, $n = 402$). Finally, we examined self-reported reasons for substitution and associations between substitution and quantity of cannabis use. Logistic regression analyses were used to examine the associations between these variables and dichotomous indices of (presence/absence) the three types of substitution. All significance tests were two-tailed.

Results

Substituting cannabis for one or more of alcohol, illicit drugs, or prescription drugs was reported by 87% ($n = 410$) of respondents, with 36% ($n = 168$) substituting cannabis for only one class of substances, 25% ($n = 118$) substituting for two classes, and 26% ($n = 124$) substituting for all three classes. Examination by class of drug (Table 2) identified substitution for prescription drugs as the most commonly reported form of substitution (80%), followed by alcohol (52%), and illicit substances (33%). The most commonly endorsed reasons for substitution were ‘less adverse side effects’ (51%, $n = 208$), followed closely by ‘better symptom management’ (49%, $n = 199$).

Amount used

Median weekly amount of cannabis used was 14 g. Comparisons based on a median split of higher versus

lower quantity users indicated that quantity of use was not associated with differences in the observed levels of any of the three forms of substitution; for prescription drugs [odds ratio (OR) = 0.77, 95% confidence interval (CI) = 0.44–1.37], alcohol (OR = 1.44, 95% CI = 0.95–2.19) or illicit drugs (OR = 0.93, 95% CI = 0.60–1.45).

Medical condition

Participants who identified pain-related conditions as the primary reason for using CTP were more likely to report substituting cannabis for prescription drugs (OR = 1.99, 95% CI = 1.23–3.21), but did not differ with regard to rates of substituting cannabis for alcohol (OR = 1.01, 95% CI = 0.76–1.59), or illicit substances (OR = 0.96, 95% CI = 0.65–1.42). Supplementary analyses comparing those who endorsed pain as a symptom treated with CTP to those who listed a non-pain-related primary condition treated with CTP produced a parallel pattern of results: those who used CTP to treat pain were more likely to substitute cannabis for prescription drugs (OR = 1.92, 95% CI = 1.12–3.30), and did not differ from respondents who did not endorse CTP use for pain with regard to substituting cannabis for alcohol (OR = 1.03, 95% CI = 0.64–1.66) or illicit substances (OR = 1.30, 95% CI = 0.77–2.20). Participants who used CTP primarily to treat depression or anxiety did not differ from other participants with regard to prescription drugs (OR = 1.49, 95% CI = 0.77–2.89), alcohol (OR = 1.35, 95% CI = 0.83–2.19), or illicit substances (OR = 1.43, 95% CI = 0.87–2.35).

Authorisation

Comparison of authorised versus unauthorised status indicated that authorised users (Table 2) were marginally less likely to substitute cannabis for alcohol (OR = 0.63, 95% CI = 0.43–0.93), and did not differ with regard to substituting for prescription drugs (OR = 1.45, 95% CI = 0.87–2.41), or illicit substances (OR = 0.92, 95% CI = 0.61–1.39).

Affordability

Respondents who reported substituting cannabis for prescription drugs were moderately more likely to report difficulty affording sufficient quantities CTP (OR = 0.59, 95% CI = 0.37–0.94). Affordability was not related to substitution for alcohol (OR = 0.75, 95% CI = 0.52–1.08) or for illicit substances (OR = 1.01, 95% CI = 0.68–1.49).

Table 2. Patients who report substituting cannabis for alcohol and other drugs by condition, authorisation, affordability, addiction treatment, and age

	Medical condition		Authorisation		Affordability		Addiction treatment history		Age		
	All	Pain	Other	Authorised	Unauthorised	No	Yes	No	Yes	Younger	Older
R _x (%)	80	86**	75**	84	79	84*	76*	80	85	84**	76**
Alcohol (%)	52	53	51	44*	55*	55	48	52	51	62**	41**
Illicit (%)	33	32	33	31	33	33	33	29**	54**	37**	26**

Note: R_x = prescription drugs; affordability: no = *sometimes* or *never* afford cannabis for therapeutic purposes (CTP), yes = *always* or *often* afford CTP; age: younger = <40 years old, older = ≥40 years old; groups differences **P* < 0.05, ***P* < 0.01 (two-tailed).

Addiction treatment history

Comparison according to any history of treatment for problematic substance use indicated that those who had a history of treatment exhibited higher levels of substituting cannabis for illicit substances (OR = 2.16, 95% CI = 1.52–3.06), but did not differ from those without a treatment history with regard to substituting cannabis for alcohol (OR = 1.01, 95% CI = 0.73–1.40) or for prescription drugs (OR = 1.37, 95% CI = 0.84–2.21).

Age

Respondents who substituted cannabis for prescription drugs were younger [M = 38.58 standard deviation (SD) = 12.57] than those who did not engage in this class of substitution [M = 44.26 (SD = 13.90)], (OR = 0.97, 95% CI = 0.95–0.99). Similarly, respondents who substituted cannabis for alcohol were younger [M = 36.65 (SD = 12.99)] than those who did not engage in this class of substitution [M = 42.84 (SD = 12.26)], (OR = 0.96, 95% CI = 0.95–0.98), and respondents who substituted cannabis for illicit substances [M = 36.50 (SD = 12.55)] were younger than those who did not engage in this class of substitution [M = 41.13 (SD = 13.01)] [M = 42.84 (SD = 12.26)], (OR = 0.97, 95% CI = 0.96–0.99).

Discussion

The results of this study are consistent with a growing body of research suggesting that cannabis use may play an important role in the use of prescription drugs, alcohol and illicit substances. Although we identified generally high rates of substitution across all patients, we also identified variability in rates of substitution across substances and contextual factors. Specifically, using cannabis for pain relief was associated with substituting cannabis for prescription medications; having a history of treatment for substance use was associated

with substituting for illicit substances; and younger age was associated with higher rates of substitution across all substances. We also found that respondents who used CTP without authorisation were more likely to use cannabis as a substitute for alcohol, whereas those substituting cannabis for prescription drugs were more likely to have difficulty affording cannabis.

The high rate of substitution for prescribed substances, particularly among patients with pain-related conditions, suggests that further research into cannabis/cannabinoids as a potentially safer substitute for or adjunct to opiates is justified, and adds to research suggesting this phenomenon is robust across samples [6,20]. This includes a study by Bachhuber *et al.* that examined the association between the medical cannabis laws in US states and opiate overdose deaths, which found nearly 25% lower mean annual rates of opioid overdose mortality among states that allowed medical cannabis, noting that the protective influence of medical cannabis regulation grew stronger over time [33]. The recent rise of addiction to pharmaceutical opiates in Canada and around the world and an associated increase in opiate-related morbidity and mortality [34–36] highlights the importance of exploring this context for substitution and its potential public health impacts.

The finding that cannabis was substituted for alcohol and illicit substances suggests that the medical use of cannabis may play a harm reduction role in the context of use of these substances, and could have implications for substance use treatment approaches requiring abstinence from cannabis in the process of reducing the use of other substances. Furthermore, public policies informed by evidence that cannabis might be a substitute for alcohol [12,18,23,37] could have an impact on overall rates of alcoholism, as well as alcohol-related automobile accidents, violence, and property crime [38].

The novel finding that patients under 40 reported a higher rate of substitution than older patients poten-

tially reflects more established patterns of substance use among older patients. In addition, younger patients typically use more psychoactive substances in the first place, leading to greater opportunities for substitution [30]. This finding suggests that older patients might benefit from education regarding the potential of cannabis to serve as a substitute for prescription drugs, alcohol, and illicit substances and indicates that future research on cannabis substitution should consider the age of the sample.

The finding that higher rates of substituting cannabis for prescription drugs was associated with lower ability to afford cannabis warrants consideration, and may reflect increased demand—and therefore higher cost—for cannabis related to use for this purpose. Such an interpretation is consistent with our finding that affordability was inversely associated with substitution of prescription medications, as such medications are subsidised in Canada, making them generally less expensive than cannabis. In contrast, alcohol and illicit drugs may be more expensive than cannabis, and therefore substitution of cannabis for these substances would not be expected to be associated with financial stress. Indeed, as we did not find that cannabis substitution for prescription medications was associated with the use of a greater quantity of cannabis, findings related to economic pressure suggests that affordability might limit cannabis use, adding to research that highlights the importance of affordability for maximising efficient access to cannabis [25,31].

The finding of higher levels of substituting cannabis for alcohol among unauthorised users was surprising, as prior research identified few differences between authorised and unauthorised Canadians who use CTP [32]. We propose that the actual government-regulated authorisation process may have led to a formalisation of medical cannabis use among authorised patients, limiting their reported reasons for the use of medical cannabis to those recognised and approved by their physician and Health Canada. However, further research that directly queries this issue is required to confirm this hypothesis.

Limitations

The limitations of this study are common to online medical surveys, such as the potential for multiple responses from a single respondent, a potentially unrepresentative sample, and lack of physician confirmation of medical conditions. Since no data was gathered on the extent of self-reported substitution, it is not possible to determine how much actual prescription drug, alcohol or illicit drug use was substituted for, and variable time frame for retrospective reporting may impact the reliability of recall. Furthermore, response

bias related to participant self-selection and recruitment through organisations that support medical cannabis patients likely resulted in overrepresentation of individuals who respond favourably to the medical use of cannabis. 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 and biological drug testing. However, these limitations are counterbalanced by several methodological strengths, including the size of the sample, the inclusion of an in-person subsample, and adherence to established standards for reporting Internet-based surveys [39].

Conclusions

Taken together, our findings provide additional evidence for the widespread nature of cannabis substitution and suggest potentially fruitful avenues for further research that elucidates the complex interaction between cannabis use and the use of other substances. In particular, as the therapeutic and recreational uses of cannabis continue to be normalised, research that explicitly investigates contexts and motives for substitution, particularly in younger adults, might help to maximise the health benefits of this emerging phenomenon. Further research is needed to better estimate the extent of substitution, and to specify differences in substitution across prescription drugs (i.e. opiates, benzodiazepines, anti-inflammatories), and other substances such as tobacco and caffeine. To this end, we recommend the development of a psychometrically valid instrument to facilitate the reliable assessment of cannabis substitution across diverse samples, contexts and substances.

Acknowledgements

This research was supported by a grant from the UBC Institute for Healthy Living and Chronic Disease Prevention. The authors would like to thank the hundreds of Canadian medical cannabis patients who took the time to participate in this survey, and would also like to express our gratitude to Ben Atkinson and Megan Hiles for their contribution to data collection and management.

Conflict of interests

Philippe Lucas is currently employed as Vice-President, Patient Research and Services for Tilray, a federally

authorised medical cannabis company. However, he was not employed by Tilray during the preliminary planning, data collection and analysis of this study, and his compensation is not tied in any way to the outcomes of this study. None of the other authors have any conflicts of interest with regard to the contents of this paper.

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Cannabis as a substitute for prescription drugs – a cross-sectional study

James M Corroon Jr¹
Laurie K Mischley²
Michelle Sexton³

¹Center for Medical Cannabis Education, Del Mar, CA, ²Bastyr University Research Institute, Kenmore, WA, ³Department of Medical Research, Center for the Study of Cannabis and Social Policy, Seattle, WA, USA

Background: The use of medical cannabis is increasing, most commonly for pain, anxiety and depression. Emerging data suggest that use and abuse of prescription drugs may be decreasing in states where medical cannabis is legal. The aim of this study was to survey cannabis users to determine whether they had intentionally substituted cannabis for prescription drugs.

Methods: A total of 2,774 individuals were a self-selected convenience sample who reported having used cannabis at least once in the previous 90 days. Subjects were surveyed via an online anonymous questionnaire on cannabis substitution effects. Participants were recruited through social media and cannabis dispensaries in Washington State.

Results: A total of 1,248 (46%) respondents reported using cannabis as a substitute for prescription drugs. The most common classes of drugs substituted were narcotics/opioids (35.8%), anxiolytics/benzodiazepines (13.6%) and antidepressants (12.7%). A total of 2,473 substitutions were reported or approximately two drug substitutions per affirmative respondent. The odds of reporting substituting were 4.59 (95% confidence interval [CI], 3.87–5.43) greater among medical cannabis users compared with non-medical users and 1.66 (95% CI, 1.27–2.16) greater among those reporting use for managing the comorbidities of pain, anxiety and depression. A slightly higher percentage of those who reported substituting resided in states where medical cannabis was legal at the time of the survey (47% vs. 45%, $p=0.58$), but this difference was not statistically significant.

Discussion: These patient-reported outcomes support prior research that individuals are using cannabis as a substitute for prescription drugs, particularly, narcotics/opioids, and independent of whether they identify themselves as medical or non-medical users. This is especially true if they suffer from pain, anxiety and depression. Additionally, this study suggests that state laws allowing access to, and use of, medical cannabis may not be influencing individual decision-making in this area.

Keywords: cannabis, marijuana, prescription drugs, pain, analgesics, opioid

Introduction

The past two decades have brought about a prodigious change in state laws and social policies regarding the use of cannabis for medical and other purposes. Twenty-eight states and the District of Columbia currently enforce legalized medical cannabis laws. Eight of these states and the District of Columbia have also legalized cannabis for recreational use.¹ Among other factors, these legislative and policy changes have resulted in shifts in social acceptance and cannabis use patterns in the US population, some of which have been driven by a growing understanding of the medicinal value of cannabis.²

Correspondence: James M Corroon Jr
Center for Medical Cannabis Education,
428 8th Street, Del Mar, CA 92014, USA
Tel +1 858 367 0393
Email jamie@corroon.com

According to the Center for Behavioral Health Statistics and Quality (CBHSQ), past-month use of cannabis has risen steadily each year in the general population from 5.8% in 2007 to 8.4% in 2014. In 2015, an estimated 22.2 million of >265 million Americans aged ≥ 12 years reported having used cannabis in the past month (8.3%).³

In addition to changing use patterns, recent research suggests that physicians' drug prescribing patterns may also be changing in states with legalized medical cannabis. Bradford and Bradford⁴ reported a drop in filled prescriptions in such states between 2010 and 2013 for drugs under Medicare Part D for the treatment of conditions such as pain, anxiety, depression and others. The US Centers for Disease Control and Prevention (CDC) has issued federal guidelines on the long-term use of opiates, noting concerns that there may be negative unintended consequences associated with dose reduction, such as patients switching to the use of heroin.⁵ An alternative for patients with chronic pain is switching to the use of cannabis to navigate dose reduction and to treat their pain and/or comorbid conditions outright.⁶ A recent open-label, prospective study suggests that medical cannabis may decrease opioid use and benefit patients with treatment-resistant pain.⁷

Here, we analyzed self-reported data for frequency of prescription drug substitution with cannabis use across sociodemographic characteristics, prescription drug class, state legalization policies for medical cannabis and global quality of life health scores.

Methods

Survey

The institutional review board (IRB) of Bastyr University approved the protocol. Procedures were in accordance with the ethical standards of the Declaration of Helsinki, as revised in 2008. Documentation of consent was waived in accordance with Department of Health & Human Services regulation 45 CFR 46.117(c) by the IRB of Bastyr University on the basis that the research presents no more than minimal risk of harm. The only record linking the subject with the research would be the consent document, and thus, the principal risk would be potential harm resulting from a breach of confidentiality. A literature review was conducted to identify existing epidemiological surveys of cannabis use.⁸⁻¹³ The authors developed a novel questionnaire by assessing the strengths and weaknesses of existing surveys to meet the goals of this study. Drafts were circulated to physician researchers and cannabis users for feedback in an iterative process. The final survey consisted of 44 structured questions answered by yes/no, multiple choice, open-ended

response fields and rating scales.¹⁴ These included patient-reported outcomes (PROs) using the PROMIS® Global Health 10-item short form (part of a National Institutes of Health [NIH] initiative to produce validated, self-reported item banks for physical, mental, emotional and social health) to measure overall well-being. Study data were collected and managed using Research Electronic Data Capture (REDCap), a secure tool allowing participants to directly enter responses.¹⁵

Subjects were a self-selected convenience sample who accessed the survey through links posted on the Center for the Study of Cannabis and Social Policy and Bastyr University websites, a Facebook page, flyers in Washington State cannabis dispensaries or word of mouth from December 2013 to January 2016. Recruitment strategies included Bastyr University medical students circulating the survey through their own social media, by distributing IRB-approved fliers to local medical cannabis dispensaries in Washington State, through public lectures describing the questionnaire at King County Library Systems locations, in an article written for an online Cannabis magazine and through an article posted to an online group located at momswithms.org. The only inclusion criterion was having used cannabis at least once in the past 90 days. A total of 31 respondents from the 2,864 respondents were deemed ineligible and excluded based on this criterion. Another 14 were excluded for failure to answer the eligibility question. To minimize risk to participants, no identifying information was collected. Individuals were given the opportunity to provide a five-digit code that enabled repeat responses to be identified with only the first response analyzed. A total of 389 (10.4%) individuals failed to provide this code and were included in the final analysis. A total of 45 repeat responders were identified and deleted, leaving a total of 2,774 eligible respondents. Individuals were told that they could skip any question(s) they did not wish to answer. Those who refused to provide a five-digit code were included based on the rationale that fear of lost anonymity is more likely to motivate response refusal than repeat participation.

Data sources and measurement

Prescription drug substitution was evaluated by asking survey respondents, "Have you ever used cannabis as a substitute for prescription drugs (yes/no)?" If the respondent answered in the affirmative, an open-ended response field was available with the instructions, "Please list prescription drugs that you have substituted cannabis for:"

If a specific number of prescription drugs were entered into the open-ended response field, values were coded as the

number of drugs per category. For example, “opiate pain killers (Roxicet, Percocet, Vicodin) and benzos (Xanax)” was counted as three substitutions in the drug category of narcotics/opioids and one substitution in the drug category of benzodiazepines. If a specific number of prescription drugs were not entered, values were coded as the number of drug categories. For example, “opiates and pain killers, muscle relaxants, anti-anxiety meds and depression meds” was counted as one substitution for the following four drug categories: narcotics/opioids, muscle relaxants, anxiolytics and antidepressants.

All nonspecific drug entries mentioning “anxiety” (e.g., “anxiety meds”) were categorized as anxiolytics and then combined with drugs in the benzodiazepines category to form the broader category of anxiolytics/benzodiazepines. Combination drugs were recorded in multiple categories where appropriate, except for combinations of opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Generic values like “pain medicine” were categorized as narcotics/opioids, as opposed to NSAIDs/non-opioid analgesics. Generic values like “prescription headache medication” were categorized as anti-migraine, despite the absence of language confirming the headaches were actually migraines.

Drugs available over the counter (OTC), and entered with specific names, were recorded as prescription drugs. For example, “ibuprofen” was assumed to be prescription ibuprofen, given the nature of the question(s) in the survey.

Type of cannabis use was determined by asking the question, “What kind of user do you consider yourself to be?” Respondents were given four, non-mutually exclusive options: “recreational user”, “medically indicated, recommended by licensed provider”, “medically indicated, self-prescribed” and “religious (e.g., Rastafari)”. For the purposes of this analysis, medical cannabis users were defined as those respondents identified as either “medically indicated, recommended by licensed provider” or “medically indicated, self-prescribed”, including those who were also identified as a “recreational user”.

Data analyses

Data analyses were conducted using SAS University Edition (SAS 9.4; SAS Institute Inc., Cary, NC, USA). Univariate and bivariate comparisons were conducted using PROC FREQ and chi-square tests. Odds ratios (ORs) were used to estimate strength of association using PROC LOGISTIC. Patient-Reported Outcomes Measurement Information

System (PROMIS) scores were calculated using the recommended scoring method that calibrates each score to a US national mean of 50 and standard deviation (SD) of 10.¹⁶ T-scores were calculated for only those respondents who answered all questions of the short form. Mean differences between PROMIS mental health and PROMIS physical health scores were computed using a two-sample *t*-test using PROC TTEST. Statistical significance was assessed using an alpha value of 0.05. Figures were produced using Microsoft Excel for Mac, version 15.27.

Results

Demographics

A total of 2,774 respondents were included in the final study population. A majority of respondents were males (55.72%), aged <36 years (62.71%), Caucasian (86.13%), residing in the US (83.02%) and identifying themselves as medical cannabis users (59.81%; Table 1). All 50 US states and >42 countries were represented in the survey. Just over half of respondents reported residing in the following states: Washington (32.50%), California (8.47%), Oregon (5.89%) or Colorado (4.27%).

A total of 1,248 respondents, or ~46% of respondents, responded affirmatively to the question, “Have you ever used cannabis as a substitute for prescription drugs?” The odds of reporting substituting cannabis for prescription drugs increased with age, up to 65 years of age (Table 2). The odds of reporting substituting were 1.21 (95% confidence interval [CI], 1.04–1.40) greater among females than males and 1.58 (95% CI, 1.00–2.48) greater among Native American/Asian/Pacific Islanders than Caucasians. Geographically, the odds of reporting substituting were greater among those residing in Canada (OR, 1.20; 95% CI, 0.82–1.76) and lesser among those residing in Europe (OR, 0.93; 95% CI, 0.72–1.21) as compared to those residing in the US. These geographical comparisons were not statistically significant.

Substitution for prescription drugs

A total of 1,248 respondents reported a total of 2,473 substitutions of prescription drugs. This represents approximately two drug substitutions per affirmative respondent. The most common classes of drugs substituted were narcotics/opioids (35.8%), anxiolytics/benzodiazepines (13.6%) and antidepressants (12.7%; Figure 1). Substituting cannabis for narcotics/opioids was 2.6 times more frequent than substituting cannabis for anxiolytics/benzodiazepines, the second most commonly substituted drug category.

Table 1 Sociodemographic characteristics of survey respondents during 2016 (n=2,774)

Characteristic	n (%)
Gender	
Male	1,529 (55.72)
Female	1,215 (44.28)
Missing	30
Income: last 12 months	
<\$20,000	548 (20.45)
\$20,000–40,000	644 (24.03)
\$40,000–60,000	456 (17.01)
\$60,000–80,000	298 (11.12)
\$80,000–100,000	258 (9.63)
\$100,000–150,000	268 (10.00)
>\$150,000	208 (7.76)
Missing	94
Highest level of education	
Less than eighth grade	9 (0.33)
Grade 9–11	90 (3.28)
High school/GED	771 (28.14)
Technical school	307 (11.20)
Associate	404 (14.74)
Bachelors	793 (28.94)
Masters	234 (8.54)
Doctorate	132 (4.82)
Missing	34
Age (years)	
≤21	453 (16.62)
22–35	1,256 (46.09)
36–50	601 (22.06)
51–65	361 (13.25)
>65	54 (1.98)
Missing	49
Current employment	
Full time	1,425 (52.10)
Part time	577 (21.10)
Unemployed	372 (13.60)
Retired	116 (4.24)
Disabled	245 (8.96)
Missing	39
Race/ethnicity	
Caucasian	2,354 (86.13)
Black/African–American	45 (1.65)
Hispanic	99 (3.62)
Native American	36 (1.32)
Asian/Pacific Islander	43 (1.57)
Other	156 (5.71)
Missing	41
Geography	
US	2,234 (83.02)
Canada	110 (4.10)
Europe	266 (9.90)
Other	81 (3.01)
Missing	83
Type of user	
Medical	1,659 (59.81)
Non-medical	1,115 (40.19)
Have you ever used cannabis as a substitute for prescription drugs?	
Yes	1,248 (45.55)
No	1,492 (54.45)
Missing	34

Abbreviation: GED, General Educational Development.

Table 2 Odds of reporting ever having used cannabis as a substitute for prescription drugs by sociodemographic characteristics during 2016 (n=2,740)

Characteristic	Yes (n=1,248)	No (n=1,492)	OR (95% CI)
	n (%)	n (%)	
Age (years)***			
≤21	185 (41.29)	263 (58.71)	1.00 (reference)
22–35	542 (43.29)	710 (56.71)	1.09 (0.87–1.35)
36–50	300 (50.59)	293 (49.41)	1.46 (1.14–1.86)
51–65	190 (53.52)	165 (46.48)	1.64 (1.24–2.17)
>65	16 (31.37)	35 (68.63)	0.65 (0.35–1.21)
Missing	15	60	
Gender*			
Male	661 (43.63)	854 (56.37)	1.00 (reference)
Female	581 (48.30)	622 (51.70)	1.21 (1.04–1.40)
Missing	6	50	
Race/ethnicity			
Caucasian	1,064 (45.65)	1,267 (54.35)	1.00 (reference)
Black/African American/Hispanic	64 (44.44)	80 (55.56)	0.95 (0.68–1.34)
Native American/Asian/Pacific Islander	45 (56.96)	34 (43.04)	1.58 (1.00–2.48)
Other	65 (42.48)	88 (57.52)	0.88 (0.63–1.22)
Missing	10	57	
Geography			
US	1,002 (45.50)	1,200 (54.50)	1.00 (reference)
Canada	55 (50.00)	55 (50.00)	1.20 (0.82–1.76)
Europe	116 (43.77)	149 (56.23)	0.93 (0.72–1.21)
Other	40 (50.00)	40 (50.00)	1.20 (0.77–1.87)
Missing	35	82	
Type of user			
Non-medical	269 (24.43)	832 (75.57)	1.00 (reference)
Medical	979 (59.73)	660 (40.27)	4.59 (3.87–5.43)
Missing	0	0	

Notes: p-values for the above comparisons were the result of chi-square analyses. * $p<0.05$ and *** $p<0.001$.

Abbreviations: OR, odds ratio; CI, confidence interval.

Medical versus non-medical users

The odds of reporting substituting were 4.59 (95% CI, 3.87–5.43) times greater among self-identified medical cannabis users as compared to non-medical cannabis users. Approximately one-quarter (24.43%) of non-medical users reported substituting cannabis for prescription drugs (Table 2).

The relationship between user type (ie, medical or non-medical) and frequency of reported substitution was assessed independently for males and females and for different categories of age. The odds of substituting were more than six times greater (OR, 6.09; 95% CI, 4.65–7.80) among female medical users than among female non-medical users. Similarly, the odds were 3.7 times (95% CI, 2.91–4.57) greater among male medical users. A trend in the odds of substituting among medical users was also seen with increased age (Table 3).

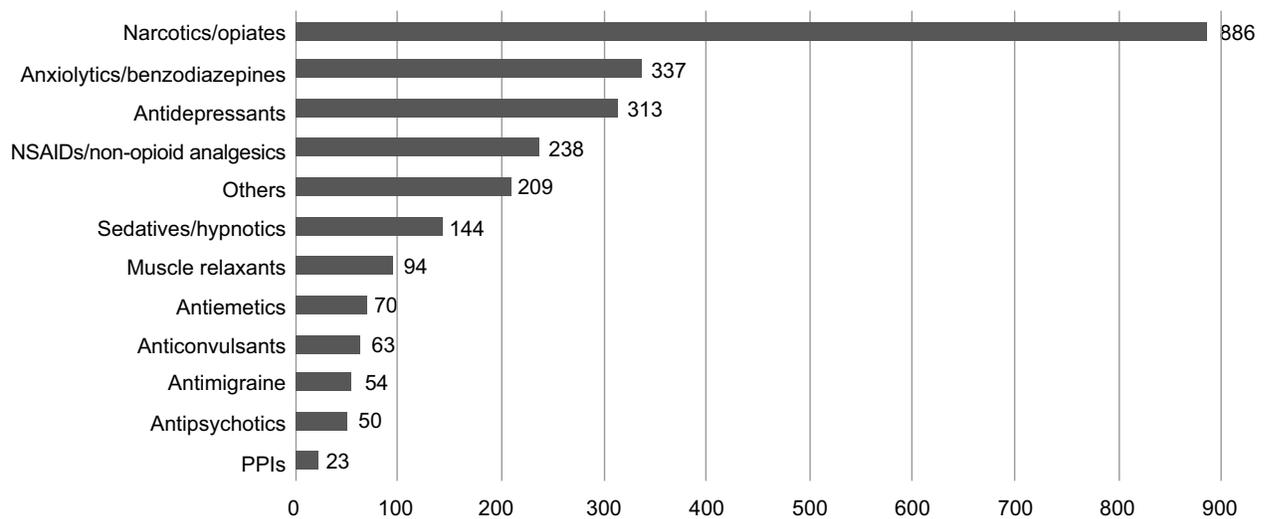


Figure 1 Number of reported prescription drug substitutions, by drug category, during 2016 (n=2,473).

Abbreviations: PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 3 ORs and 95% CIs of reporting ever having used cannabis as a substitute for prescription drugs by user type, stratified by selected sociodemographic characteristics, during 2016 (n=2,740)

Characteristic	Medical user, OR (95% CI)
Gender	
Female	6.09 (4.65–7.80)
Male	3.67 (2.91–4.57)
Age (years)	
≤21	4.79 (3.20–7.18)
22–35	3.72 (2.92–4.73)
36–50	5.32 (3.63–7.78)
51–65	16.19 (6.75–38.79)
>65	NA

Notes: Reference, non-medical user. NA, insufficient data in one cell.

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable.

Comorbidities

We previously reported in an earlier survey that of 1,429 respondents, 61% reported using cannabis for managing pain, 58% reported using cannabis for anxiety and 50% reported using cannabis for depression.⁶ In the current analysis, these same conditions were also the most commonly reported conditions by respondents. Of the 1,040 participants reporting pain and/or intractable pain, 619 (59.52%) reported depression and anxiety as comorbidities. As such, the odds of reporting substituting cannabis for prescription drugs were more than one and a half times greater (OR, 1.66; 95% CI, 1.27–2.16) among those reporting using it to manage pain, anxiety and depression than among those using it to manage only one of the three conditions.

States with legalized medical marijuana

A slightly higher percentage of those who reported substituting resided in states where medical cannabis was legal at the time of the survey (47% vs. 44%, $p=0.47$). This difference was not statistically significant.

PROMIS Global Health

The 10-item short form developed and published by PROMIS was used to arrive at a bottom-line indicator of self-reported health status. By summing the physical and mental health scores separately (using only participants with complete data on each subscale), the standard PROMIS raw score to T-score conversion allowed for comparing our sample with the general population. The distributions are standardized such that a score of 50 represents the mean for the US general population, with an SD of 10 points. A total of 1,186 respondents (43%) provided complete information for the 10-item short form. For mental health, the sample scored 39.34 (SD=5.05; 95% CI, 39.15–39.53). For physical health, the sample scored 40.26 (SD=3.94; 95% CI, 40.11–40.41), placing these respondents below average for global mental health and global physical health as compared with the general population. Those reporting substituting cannabis for prescription drugs scored similar to the overall sample population (mental health, mean: 39.75 [SD=5.32; 95% CI, 39.45–40.05]; physical health, mean: 39.80 [SD=4.00; 95% CI, 39.57–40.02]). In terms of the PROMIS raw scores (i.e., non-T-score-converted scores), those who reported substituting had slightly higher mental health scores (mean difference: 0.31; $p<0.001$) and slightly lower physical health scores

(mean difference: -0.31 , $p < 0.001$) than those who denied substituting (Figure 2).

Sensitivity analysis

A total of 389 respondents failed to provide a 5-digit code anonymously identifying themselves as unique respondents. When excluded from the analysis, the percentage of respondents reporting ever using cannabis as a substitute for prescription drugs increased from 45.55% ($n=1,248$) to 46.28% ($n=1,094$), an increase of 1%.

The odds of reporting substituting among medical users versus non-medical users decreased from 4.59 (95% CI, 3.87–5.43) to 4.54 (95% CI, 3.78–5.45), a decrease of 1.5%. Finally, while the total number of prescription drug substitutions by drug category decreased from 2,473 to 2,160, the per respondent substitution ratio remained two substitutions per respondent.

Discussion

The purpose of this study was to examine whether, and how often, cannabis users report substituting cannabis for prescription drugs. Overall, these PROs underscore four key points: 1) individuals are substituting cannabis for prescription drugs, independent of whether they identify themselves as medical users (medical users are doing so at almost five times the odds of non-medical users) and independent of legal access to medical cannabis; 2) this practice increases in frequency with age, up to 65 years, and is more common in females, particularly female medical users, and Native American/Asians/Pacific Islanders; 3) the most common classes of substitution were narcotics/opioids, anxiolytics/benzodiazepines and antidepressants; and 4) the odds of reporting substituting cannabis for prescription drugs were

more than one and a half times greater among those reporting the use of cannabis to manage pain, anxiety and depression than among those using it to manage only one of these three conditions. Stated differently, pain, anxiety and depression seem to represent a comorbidity triad that is associated with greater substitution frequency.

These data are in line with previous research suggesting that cannabis is commonly used as a substitute for prescription drugs. For example, in 2013 and 2016, Lucas et al^{17,18} found that 68% of 259 and 87% of 410 physician-authorized medical cannabis users in Canada reported substituting cannabis for alcohol and illicit or prescription drugs, respectively. In 2017, Lucas and Walsh¹⁹ found that 63% of 271 such subjects reported substituting cannabis for prescription drugs such as opioids (30%), benzodiazepines (16%) and antidepressants (12%), representing the same top three categories as data presented here. These findings also agree with our previous data showing that medical cannabis users report using cannabis most frequently to manage pain, anxiety and depression.⁶ The present study contributes to a greater understanding of substitution across specific classes of prescription drugs in a largely US-based sample, in a much larger cohort and cross-section, occurring among both medical and non-medical subjects, and in areas without legal access.

While the results of research on the effects of cannabis for medical use have been largely mixed, our previous study indicated that patients reporting using cannabis for managing pain are experiencing adequate symptom relief.⁶ In 2016, Boehnke et al conducted a survey at a medical cannabis dispensary and found a 64% decrease in opioid use among those reporting using cannabis for chronic pain ($n=118$). Respondents also reported a reduction in other classes of drugs, including antidepressants and NSAIDs, as well as a

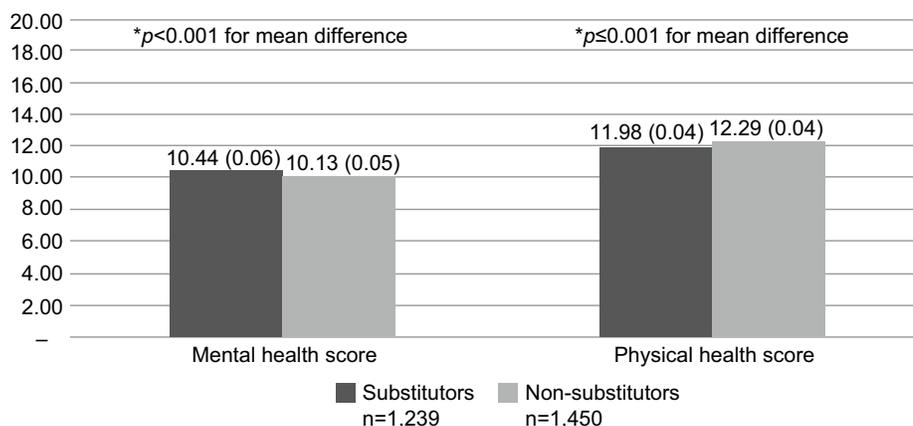


Figure 2 PROMIS Global Health short form: physical and mental health scores (mean [SE]; cannabis substitutors versus non-substitutors, 2016; raw scores [i.e., non-T-score corrected]).

Notes: Maximum score=20 for each domain. High scores reflect better functioning.

Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

decrease in the number of side effects of medications.²⁰ This study highlights differences between those with the comorbidities of pain, anxiety and depression and those with only one of the morbidities.

This team previously reported that in a survey of 1,429 medical cannabis users, 61% reported cannabis use for pain, 58% reported cannabis use for anxiety and 50% reported using cannabis to manage depression.⁶ In 2016, Dale and Stacey²¹ reported that those using cannabis for pain were more likely to be substituting for prescription drugs. In 2017, Walsh et al published a review of medical cannabis and mental health to try to better understand how medical cannabis use may impact areas of potential concern for clinicians. “Relaxation and relief of anxiety” and “relief of negative mood” or depression were among the most widely reported conditions in 60 publications included in their analysis.²² Because it is common for chronic pain patients to be prescribed combinatorial pharmacotherapy to address comorbidity with depression and/or anxiety, it is largely unknown how often patients may be discontinuing prescription medications when initiating cannabis use.²¹ Doctors need to have open communication with their patients regarding these matters in order to ensure that the medical community does not repeat the prescribing mistakes made in the past with opioid pharmacotherapy, namely, unchecked use of medical cannabis that leads to adverse events and abuse.²³ Furthermore, these preliminary data can serve to drive prospective research focused on whether cannabis can assist in opioid tapering protocols so that doctors can offer patients science-based guidance.

Importantly, older individuals may be substituting cannabis for prescription drugs at a higher rate than the general population, a finding in line with previous research.⁴ There are very little data on the impact of cannabis use in elderly populations. Our data show a trend toward increased substitution with age, perhaps not surprisingly, as older populations are more likely to be prescribed prescription drugs, particularly psychotropic medications.^{24,25}

We previously reported that medical cannabis users are evaluating cannabis products for the presence of a secondary, non-intoxicating cannabinoid, cannabidiol (CBD), ~40% of the time.⁶ CBD does not have the same action at the cannabinoid receptor as Δ^9 -tetrahydrocannabinol (THC), the primary intoxicating constituent in cannabis. To avoid adverse effects, particularly in elderly populations, the application of CBD-dominant cannabis varieties and preparations may be warranted. There is a need for more research on mental health disorders and cannabis use, particularly with a focus

on CBD rather than THC-dominant cannabis.²² This information is needed for doctors to be able to adequately participate in conversations with their patients, regardless of age, about the role that medical cannabis may play in managing mental health conditions.²⁶

We previously reported on gender differences in cannabis use and effects, highlighting the need for focused research on this topic.²⁷ Importantly, there is evidence of differences in endocannabinoid system function across gender.^{28–30} Here, we report that female users may be more likely to substitute cannabis than male users (OR, 1.21; 95% CI, 1.04–1.40) and that female medical users may be much more likely to substitute cannabis than female non-medical users (OR, 6.09; 95% CI, 4.65–7.80). These findings are interesting given that females reported significantly less frequency and quantity of use in our previous study. In that study, women were more likely to report use for anxiety, nausea, anorexia and migraine headaches than men. Taken together, these findings provide preliminary data for future studies on gender-based differences in cannabis use and effects.

This study showed a nonsignificant difference between the proportion of individuals reporting substituting cannabis for prescription drugs in states with legalized medical cannabis versus states where cannabis remains illegal (47% vs. 44%, $p=0.47$). This finding suggests that state laws allowing access to, and use of, medical cannabis may not be influencing individual decision making in this area. This finding is in contrast to other studies showing that the use of prescription drugs fell in states once medical cannabis laws were implemented.⁴ This finding has public health implications and should be explored further.

As compared with the general population, survey respondents scored below average for global mental health and global physical health on the PROMIS 10-item short form. This association deserves further attention to determine whether individuals with lesser mental/physical health are using cannabis as a medical therapy or whether cannabis use is negatively affecting mental/physical health.

Given the current nationwide epidemic of prescription opioid-related abuse, addiction and death, there is an urgent need for alternatives with efficacy and safer toxicology profiles.³¹ It is important to note that active “substitution” with cannabis may be a conscious decision to reduce harm caused by narcotics.³² Not only may opioid therapy prove ineffective for some patients but it may also induce serious adverse reactions that complicate management, including allodynia or opioid-induced hyperalgesia, also known as “paradoxical pain”.³³ Chronic pain is an “expensive” condition, both

economically and socially, yet existing pharmacotherapeutic interventions are not always adequate.^{34–36} Taken with pre-clinical data on the role of the endocannabinoid system in stress, pain processing and immune homeostasis, it is clear that future investigation is warranted using controlled trials with human subjects to better understand the role that cannabis may play in treating pain, anxiety, depression and other conditions.^{37–46}

Limitations

The study population was a self-selected convenience sample, and it is possible that individuals with favorable opinions of, and experiences with, cannabis are more likely to have responded to the questionnaire than those with negative opinions and experiences. This, when considered with the predominance of males, Caucasians and individuals aged <35 years, indicates that our sample may not be representative of the general population. In addition, PROs are subject to reporting bias.^{47,48}

Another limitation of this study was the method by which prescription drug information was collected. The availability of an open-ended response field enabled narrative responses that made accurate categorization difficult. In some instances, this limitation may have resulted in undercounting. For example, a response of “a variety of SSRIs” was counted as one drug substitution in the drug category antidepressants. In other instances, it may have resulted in overcounting. For example, a response of “opiate pain killers (Roxicet, Percocet, Vicodin)” was counted as three substitutions in the drug category of narcotics/opioids, yet the respondent may have only substituted cannabis for “Vicodin” after previously trying “Roxicet” and “Percocet”. Additionally, drugs that are available both OTC and via prescription (e.g., ibuprofen) were counted as prescription substitutions, given the nature of the question. The substitution count for these OTC drugs would be overestimated if these drugs were not prescribed.

Data for determining the proportion of individuals reporting substituting cannabis for prescription drugs in states with legal versus illegal medical cannabis policies were analyzed as of December 31, 2016. Several states may not have had legal medical cannabis policies at the time an individual completed the survey, but did have such policies at the time of analysis, which may falsely increase the proportion of those reporting substituting in states with legalized medical cannabis.

Conclusion

These data contribute to a growing body of literature suggesting cannabis, legal or otherwise, is being used as a

substitute for prescription drugs, particularly prescription pain relievers. According to the CDC, 259 million prescriptions for pain relievers were written by health care providers in 2012.⁴⁹ In 2015, two million Americans aged ≥12 years had a substance use disorder that involved prescription pain relievers.⁵⁰ The CDC also reports that overdoses from prescription opioids are a “driving factor” in the increase in opiate overdose deaths over the past 15 years. Such deaths have more than quadrupled in the same time period with >20,000 overdose deaths attributable to prescription pain relievers alone.⁵¹

Despite the illegality of cannabis in many states and the lack of professional guidance on dosing, routes of delivery and inadequate standardization or quality control for medical use, individuals are taking it upon themselves to augment, or discontinue, US Food and Drug Administration (FDA)-approved drugs in favor of a largely unregulated herbal one.

Acknowledgment

This study was supported by NIH NCCAM K01ATTA (LKM). PROMIS was funded with cooperative agreements from the NIH Common Fund Initiative.

Disclosure

The authors report no conflicts of interest in this work.

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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

Cite as: *Can Urol Assoc J* 2014;8(11-12):e901-5. <http://dx.doi.org/10.5489/auaj.2268>
Published online December 15, 2014.

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.

Competing interests: Authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

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Correspondence: Dr. Dean A. Tripp, Department of Psychology, Queen's University, Kingston, ON K7L 3N6; dean.tripp@queensu.ca

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 (Lindsmith 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 henny ... (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.

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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

Published: 23 April 2009

Received: 3 December 2008

Substance Abuse Treatment, Prevention, and Policy 2009, **4**:7 doi:10.1186/1747-597X-4-7

Accepted: 23 April 2009

This article is available from: <http://www.substanceabusepolicy.com/content/4/1/7>

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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.

Acknowledgements

This study was made possible by grant funding from the Canadian Institutes of Health Research (CIHR) [Funding reference: MOP-77813] and career support provided by the CIHR to Dr. Johnson.

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Published in final edited form as:

Recent Pat CNS Drug Discov. 2012 April 1; 7(1): 25–40.

Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives

Simone Tambaro and **Marco Bortolato**

Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles (CA), USA

Abstract

Rich evidence has shown that cannabis products exert a broad gamut of effects on emotional regulation. The main psychoactive ingredient of hemp, Δ^9 -tetrahydrocannabinol (THC), and its synthetic cannabinoid analogs have been reported to either attenuate or exacerbate anxiety and fear-related behaviors in humans and experimental animals. The heterogeneity of cannabis-induced psychological outcomes reflects a complex network of molecular interactions between the key neurobiological substrates of anxiety and fear and the endogenous cannabinoid system, mainly consisting of the arachidonic acid derivatives anandamide and 2-arachidonoylglycerol (2-AG) and two receptors, respectively termed CB₁ and CB₂. The high degree of interindividual variability in the responses to cannabis is contributed by a wide spectrum of factors, including genetic and environmental determinants, as well as differences in the relative concentrations of THC and other alkaloids (such as cannabidiol) within the plant itself. The present article reviews the currently available knowledge on the herbal, synthetic and endogenous cannabinoids with respect to the modulation of anxiety responses, and highlights the challenges that should be overcome to harness the therapeutic potential of some of these compounds, all the while limiting the side effects associated with cannabis consumption.

Keywords

cannabis; anxiety; CB receptors; endocannabinoids; Δ^9 -tetrahydrocannabinol; cannabidiol

INTRODUCTION

Anxiety is generally defined as an emotional state characterized by maladaptive and excessive emotional responsiveness to potentially dangerous circumstances. The pathological expression of anxiety leads to enduring emotional perturbations with a consistent apprehension towards the possibility of future, vaguely defined negative events [1]. According to the current classification of anxiety disorders in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [2], the main diagnostic entities in this category are:

- *generalized anxiety disorder* (GAD), featuring general irritability, anxiety attacks, chronic apprehension/anxious expectation and secondary phobic avoidance.

- *panic disorder*, characterized by brief (2-10 min) spells of overwhelming anxiety or fear, accompanied by somatic and cognitive symptoms;
- *social anxiety disorder* (or social phobia), defined as extreme agitation in social contexts and avoidance of social situations;
- *obsessive-compulsive disorder* (OCD), characterized by recurrent and intrusive anxiogenic thoughts (obsessions), and stereotyped behaviors (compulsions) aimed at the reduction of the distress caused by the obsessions.
- *post-traumatic stress disorder* (PTSD), in which a prior intense trauma results in a long-lasting anxious response, with re-experiencing/flashback phenomena, avoidance and emotional numbing.

In keeping with their different clinical features and phenomenological presentations, these disorders are underpinned by divergent neurobiological alterations and respond to partially different pharmacotherapeutic strategies (outlined in Table 1). A fundamental contribution in our understanding of the neural bases of anxiety disorders and in the development of novel therapies has been afforded by animal models and testing paradigms for anxiety-like behaviors (summarized in Table 2).

Over the last decades, converging epidemiological, clinical and preclinical data have pointed to a key implication of cannabis and its endogenous system in the regulation of anxiety. In the following sections, we will present a brief synopsis on cannabinoids and the available classes of related agents, with a specific focus on their anxiolytic potential, and the scientific challenges that should be overcome to fully establish the applicability of such drugs in the therapy of anxiety disorders.

HERBAL AND SYNTHETIC CANNABINOIDS

Herbal cannabinoids

The three species included in the *Cannabis* genus (or sub-species, depending on the taxonomic classification; see [3], for a detailed discussion on the issue), *sativa*, *indica* and *ruderalis*, feature at least 85 unique terpenophenolic compounds, collectively named *phytocannabinoids* [4]. The main classes of phytocannabinoids are outlined in Figure 1. Quantitative analyses of cannabis constituents are usually performed by chromatographic techniques (generally Gas Chromatography, but also Thin-Layer Chromatography, or High-Performance Liquid Chromatography), often coupled with Mass Spectrometry. A detailed description of the instrumental methods used for classification and source tracing of Cannabis products (including DNA identification for forensic and intelligence purposes) is beyond the scope of this review, but can be found in [5-7].

The chemical fingerprinting of hemp products has revealed that the two most abundant phytocannabinoids are Δ^9 -tetrahydrocannabinol (THC, also named dronabinol) and cannabidiol (CBD):

The main psychoactive constituent of Cannabis, THC is a highly lipophilic alkaloid produced mainly in the leaves, flowers and glandular trichomes of the plant. Most of the pharmacological effects elicited by hemp products, including emotional and cognitive changes, analgesia, hypothermia and appetite stimulation, are considered to be reflective of the action of THC as a partial agonist of cannabinoid CB₁ and CB₂ receptors (see below). Additionally, THC has been shown to act as an acetylcholinesterase inhibitor [8-10].

In contrast with THC, CBD is not psychotropic, but has nevertheless been shown to play a role in the modulation of behavioral effects of cannabis [11]. In fact, the THC: CBD ratio is

the main criterion to define different cannabis chemotypes [12] and has been posited to contribute to the variability in neurobehavioral outcomes of marijuana or hashish consumption [13,14]. Interestingly, most cannabis strains encountered in the illegal markets generally have elevated amounts of THC [15].

The different characteristics of THC and CBD are underpinned by their distinct mechanisms of action. Whereas THC has nanomolar affinity for both CB₁ (K_i = 25.1 nmol/L) and CB₂ (K_i = 35.2 nmol/L) receptors, CBD exhibits much lower affinity for either target [16-20]; however, the latter phytocannabinoid was recently found to act as a highly potent antagonist/inverse agonist of both CB receptors [21], possibly due to a non-competitive mechanism of receptor blockade [22]. Additionally, CBD has been shown to exert some of its actions through other receptors, including the vanilloid receptor VR₁ and the serotonin receptor 5-HT_{1A} (for a general overview of the topic, see [11]).

The other main phytocannabinoids, including cannabigerol (CBG), cannabichromene (CBC) and cannabinol (CBN) (Fig. 1) [4,23], have been shown to exert antibiotic and antiinflammatory properties, but have not been strongly associated with the behavioral effects of Cannabis; nevertheless, the recent discovery that CBG is a highly potent agonist for α_2 adrenoceptor and a blocker of serotonin 5-HT_{1A} receptor [24] underscores the potential importance of these and other alkaloids in the psychoactive profile of cannabis.

Synthetic cannabinoids

In addition to phytocannabinoids, several classes of synthetic CB receptor agonists have been developed; among these families, the best characterized are the synthetic analogs of THC - such as the bicyclic compounds CP 47,497, CP 55,244, CP 55,940 and the benzopyrans HU-210 and nabilone (Fig. 2) - and the aminoalkylindole derivatives - including WIN 55,212-2, JWH-015, JWH-018, JWH-073, JWH-081 and JWH-398 (for a general review, see [23]). Of these agents, only nabilone has been approved for clinical use as an antiemetic treatment and an adjunct analgesic for neuropathic pain [25]. Other more potent synthetic cannabinoids, such as CP 47,497, HU-210 and most JWH compounds, have regrettably gained great popularity in the market of recreational substances during the last decade, under the generic brand names of “Spice” or “K2”. Unlike THC, which is a partial agonist of CB₁ receptors, these agents are full, high-potency CB₁ receptor activators [26,27], thereby eliciting greater psychotropic effects than THC (as CB₁ receptors are the key mediators of the psychotropic actions of cannabis). This characteristic, together with their legal status (recently revoked across most Western countries, including USA as of March 2011) and lack of available testing procedures for the detection of urinary metabolites, has unfortunately contributed to the great diffusion of “Spice” blends in Central and Western Europe, as well as Australasia.

ENDOCANNABINOIDS AND THEIR RECEPTORS

Following the identification of THC in the 1960s [28], extensive research was devoted to the identification of its biological targets and endogenous counterparts. Both objectives were met around 30 years later, with the characterization of the two major cannabinoid receptors, CB₁ [29] and CB₂ [30] as well as the discovery of two most prominent endocannabinoids N-arachidonylethanolamine (commonly named anandamide from the Sanskrit *nanda*, bliss) [31] and 2-arachidonoylglycerol (2-AG) [32,33] (Fig. 3).

CB receptors

Although CB₁ and CB₂ receptors only share 44% sequence identity (68% in the transmembrane domains), they are both coupled to G_{i/o} proteins [34] and activated by both anandamide and 2-AG. In line with their metabotropic nature, CB receptors mediate their

intracellular response through a number of changes affecting signaling cascades, such as inhibition of adenylyl cyclase, activation of G-protein-activated inwardly rectifying potassium channels (GIRKs) and phosphorylation of extracellular signal-related kinases (ERKs) [35,36]. The distribution pattern of CB₁ and CB₂ receptors is strikingly divergent, indicating diverse physiological functions: CB₁ is the most abundant metabotropic receptor in the brain, and is primarily distributed in the synaptic terminals of neurons across all the major structures that regulate emotional responsiveness, perception and memory, including prefrontal cortex, amygdala, septo-hippocampal system, striatum, thalamus, brainstem nuclei etc. [37-41]. CB₁ receptors are typically located on presynaptic terminals [42,43], but they have also been identified in postsynaptic locations [44,45]. Presynaptic CB₁ receptors are posited to serve critical functions for the regulation of synaptic plasticity and neurotransmitter release; in particular, they mediate the depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE), consisting in the reduction of γ -amino-butyric acid (GABA) or glutamate release, respectively, from presynaptic boutons following stimulation of the postsynaptic terminals [46-49]. In general, CB₁ activation has been shown to inhibit the neurotransmission of other mediators, including glycine, acetylcholine, norepinephrine and serotonin [50], but the underpinnings of these phenomena have not been completely elucidated. Additionally, CB₁ receptors have been implicated in short- and long-term synaptic depression, in relation to phasic or tonic endocannabinoid release (for a review on these topics, see [51]).

The function of CB₁ receptors may vary depending on the specific interactions that they entertain with other molecular targets. For example, CB₁ receptors have been found to associate with other G-protein complex receptors, such as dopamine D₂, orexin Ox1, μ opioid and adenosine A_{2a}, to form heteromeric complexes (reviewed in [52,53])

The key role of CB₁ receptors as mediators of neurochemical homeostasis in the brain is maintained through a complex regulation of their expression. For example, these receptors are subjected to a rapid internalization (via clathrin-coated pits) following their binding with full agonists; on the other hand, the receptors are also recycled, with a process that requires endosomal acidification and dephosphorilation [54].

While CB₂ receptors are abundantly expressed in most peripheral organs (and particularly in immune cells, where they regulate cytokine secretion and modulate cell trafficking) [55], their distribution in the brain appears to be sparse and particularly confined to microglial cells; nevertheless, recent evidence has revealed the presence of CB₂ receptors in several areas of the brain [56-58]. Interestingly, a number of studies suggest that neuronal CB₂ receptors may be mainly located in postsynaptic terminals [58,59]; nevertheless, the functional role of these targets in the brain remains largely elusive and awaits further characterization.

The existence of cannabinoid receptors other than CB₁ and CB₂ has been postulated based on ample experimental evidence [60-62]. Interestingly, a number of investigations have pointed to GPR55 as a novel putative cannabinoid receptor [63,64]; nevertheless, evidence on the specificity of this receptor for endocannabinoid is still inconclusive [65].

Endocannabinoids

Both anandamide and 2-AG are derivatives of arachidonic acid, an unsaturated C₂₀ fatty acid with 4 double bonds, which also serves as the precursor for synthesis of other eicosanoids, including prostaglandins and leukotriens. Anandamide is found in picomolar concentrations and acts as a high-affinity partial agonist for both CB₁ and CB₂ receptors. It is synthesized on demand by enzymatic hydrolysis of the membrane phospholipid N-arachidonoyl phosphatidylethanolamine (NAPE), a process catalyzed by several

phospholipases [66-68]. Following release and activation of CB receptors, anandamide is rapidly removed from the synaptic cleft by a carrier-mediated system [69-72] and subsequently hydrolyzed by the membrane enzyme fatty acid amide hydrolase (FAAH) [73-75]. FAAH serves the catabolism of other substrates, including oleoylethanolamine (OEA) and palmitoylethanolamine (PEA). Both these compounds do not activate CB1 receptors [76], although they may reduce or slow down anandamide degradation by competing with it for FAAH activity.

In comparison with anandamide, 2-AG is much more abundant (occurring in nanomolar concentrations across most tissues) and acts as a full agonist of both CB receptors. It is produced from 1,2-diacylglycerol (DAG) by diacylglycerol lipase (DAGL) [77] and degraded mainly by the cytosolic serine hydrolase monoacylglycerol lipase (MAGL) [78], although other enzymes are known to contribute to this process [79].

The divergent neurochemical profiles of anandamide and 2-AG underscore their different physiological roles. Although our current understanding of the different functions entertained by each endocannabinoid is still rudimentary, the development of FAAH and MAGL inhibitors [80,81] has been instrumental to elucidate the implication of each mediator in synaptic and neurochemical regulation. While 2-AG is known as the retrograde mediator of DSI [82,83] and DSE [84-87], a number of studies suggest that anandamide may serve as an activity-dependent regulator of monoaminergic transmission [88-90]. Recent evidence points to a potential biological antagonism between anandamide and 2-AG [91,92]; on the other hand, emerging evidence points to a similar role of anandamide and 2-AG in the regulation of anxiety (albeit in relation to different receptors) and pain [93]. The development of JZL195, a potent FAAH/MAGL inhibitor, has in turn revealed that the behavioral effects of CB₁ receptor agonists can be only recapitulated by the combination of both endocannabinoid-mediated functions [94].

Other lipids have been indicated as putative endocannabinoids, including 2-arachidonoylglycerylether (noladin ether) [95] and O-arachidonylethanolamine (virodhamine) [96] (Fig. 3). Additionally, recent evidence has identified that CB receptors may be modulated by peptidic ligands, such as hemopressin and its derivatives [97,98].

EFFECTS OF CANNABIS AND CANNABINOID AGENTS ON ANXIETY

Cannabis, THC and CB₁ receptor agonists

The employment of cannabis for its medicinal, relaxing and mood-enhancing properties has been documented across most ancient civilizations. Originally introduced in Chinese pharmacopoeia during the third millennium BCE [99,100], cannabis became a popular remedy throughout Asia and Europe in the following centuries [99,101]. The inclusion of cannabis in the medical treatises by Dioscorides and Galen secured the herb a stable reputation in the Roman Empire and the Arabic world [101]. Until the early 20th century, the plant remained a valuable therapy for a large number of diseases [102]; however, growing concerns about the psychoactive and narcotic effects of cannabis led to a progressive restriction and ultimate ban of its usage in the United States and several European countries [100,103]. Despite its illicit status, cannabis remains one of the most popular recreational drugs, particular among adolescents and young adults, in view of its mood-enhancing and euphoriant characteristics [104-106].

Most psychological and behavioral effects of marijuana and other hemp products are induced by THC through activation of CB₁ brain receptors. In fact, although THC and most synthetic cannabinoids are known to activate both CB₁ and CB₂ receptors, their actions on

anxiety-like behaviors and emotional regulation are efficiently countered by selective CB₁ receptor antagonists, such as rimonabant (see next section) [107].

The studies on the psychological effects of cannabis and THC have unfolded a highly complex and often contradictory scenario, fostering a long-standing debate on the potential harms and benefits of its products. An important aspect of this discussion (particularly in consideration of its legal aspects and the potential therapeutic applications of hemp derivatives), revolves around the distinction between use and misuse of cannabis. In particular, whereas the abuse and dependence liability of cannabis is generally well-recognized [108,109], the definition of these phenomena has been heavily criticized as reflective of political agendas rather than scientific bases. For instance, the diagnosis of substance abuse, according to the criteria listed by the DSM–IV TR, is based on the manifestation of at least one of four symptoms: interference with major professional or personal obligations; intoxication in hazardous settings; substance-related legal problems; continued use in the face of persistent social or interpersonal problems [110]. The applicability of some of these standards to marijuana and other cannabis derivatives, however, has been questioned [99], also in view of their lower potential to induce physical harm in comparison with other legal substances, such as alcohol and tobacco [111].

While the controversies surrounding cannabis are far from subdued (and are often permeated and masked by conflicting ideological credos), standardized studies on cannabinoids have highlighted that the psychological and behavioral outcomes of this substance are highly variable and range from relaxation, euthymia and heightened sociability to panic, paranoid ideation and psychosis [112-116]. A corollary of this observation is that the high comorbidity rate between cannabis use disorders and psychiatric conditions [100-105] may indicate that cannabis consumption is either a concurring cause or a “self-therapeutic” strategy for anxiety and mood disorders [117-123]. The latter interpretation is supported by the observation that anxiety-spectrum disturbances and traumas in early developmental stages are a strong predictor for later cannabis use disorders [124-127]; furthermore, several lines of evidence suggest that the anxiolytic effects of THC may partially account for the high prevalence of cannabis use in patients affected by PTSD [128-131] and OCD [132]. Accordingly, recent clinical studies have shown that THC elicits therapeutic effects in OCD [133] and trichotillomania, an impulse-control disorder characterized by compulsive hair-pulling [134]. Nevertheless, prospective analyses show that cannabis use and dependence increase the risk for development of panic disorder [135], suggesting that the effect of cannabis may vary with respect to the nosological entities within the spectrum of anxiety disorders. Of note, chronic consumption of cannabis has been hypothesized to exacerbate depressive or anxious manifestations, and reduce the therapeutic efficacy of anxiolytic agents [122,136-138]; an interesting theoretical implication of this finding is that long-term exposure to cannabinoid agents may lead to profound alterations of synaptic plasticity and neurochemical homeostasis and alter the pathophysiological trajectory of anxiety and mood disorders. Thus, while cannabis may be initially used as a self-therapy for certain anxiety disorders, the prolonged exposure to this substance in vulnerable individuals may in turn alter or aggravate the clinical course of these conditions and render the patients refractory to standard treatments.

The ability of cannabis to either exacerbate or attenuate emotional reactivity is highly influenced by numerous factors, including its chemotype, as well as the influence of genetic, developmental and contextual variables. Unfortunately, little is still known about the susceptibility factors that govern the behavioral outcomes of cannabis in patients affected by anxiety-spectrum disorders. Indeed, several components have been shown to play a role in this link, including genetic background, age, gender, environmental stress and concurrent

use of other drugs; a detailed analysis of these determinants is outside the scope of the present work, but the interested reader should refer to [139].

Aside from the influence of vulnerability factors, the available evidence indicates that cannabis, THC and other CB₁ receptor agonists exercise a bidirectional influence on anxiety responses as a function of the dosage. The majority of users report that consumption of modest amounts of cannabis and CB₁ receptor agonists results in euphoria, relaxation, heightened perception, sociability and creativity, moderate to high doses have been reported to elicit phobia, agitation, panic, dysphoria, psychotic manifestations and cognitive impairments [112-116,124,140-143]. In line with these premises, early studies showed a robust anxiolytic efficacy of low-dose nabilone in comparison with placebo [144,145]. Additionally, the few available reports on the clinical outcomes of recreational cannabinoids show that a moderate consumption of “Spice” blends is generally associated with euphoria and disinhibition [146], but the abuse of these substances is conducive to high levels of anxiety, panic, paranoid ideation and mood disturbances [147-151].

The biphasic effects of cannabinoids on anxiety-related responses have been extensively documented in rodents. In agreement with human evidence, preclinical studies have elucidated that the acute administration of low doses of CB₁ receptor agonists elicits anxiolytic-like in approach/avoidance tasks [152-156]; conversely, high concentrations of the same compounds are generally associated with the opposite outcomes [157-162] (for complete reviews of the topic, see [163,164])

The bidirectional action of CB₁ receptors on anxiety responses may be related to the modulatory role of these targets on GABA and glutamate release across amygdala and other forebrain areas [41,165,166]. As these two major neurotransmitters affect anxiety in an opposite fashion, different doses of cannabinoids and synthetic CB₁ receptor agonists may indeed produce highly divergent effects, in relation to their ability to affect the homeostasis and the balance of GABA and glutamate (for a review on these issues, see [163]). Furthermore, CB₁ receptors have been shown to play critical roles in the regulation of most neurochemical substrates of anxiety, including the neurotransmitters serotonin, norepinephrine and acetylcholine, as well as stress hormones, colecystokynin and opioid peptides [50,163].

In line with this concept, the infusion in the periaqueductal grey of arachidonyl-2-chloroethylamide (ACEA), an anandamide synthetic analog with high CB₁ receptor selectivity, elicited anxiolytic-like effects in rats in an elevated plus maze, with a bell-shaped dose-response curve [167], the highest doses being associated to no significant behavioral change. Novel categories of compounds have been patented for potential efficacy as selective CB₁ receptor modulators, including sulfonyl-benzamides [168] and tetrasubstituted imidazole derivatives [169]. To the best of our knowledge, however, no findings on the action of these compounds in anxiety regulation have been reported to date.

CB₁ receptor antagonists/inverse agonists

The cannabinoid CB₁ receptor antagonists/inverse agonist rimonabant was introduced into clinical practice by Sanofi-Aventis in 2006 as a treatment for obesity [170] and smoking cessation [171]. The majority of preclinical studies found that these compounds are anxiogenic at high doses [158,159,172,173] and ineffective at low doses [174,175]. The anxiogenic properties of CB₁ antagonists, were unequivocally confirmed by clinical data on the psychiatric side effects of rimonabant. The significant increase in anxiety, depression and suicidality in patients under treatment with rimonabant [176-179], in particular, led to the withdrawal of the drug from the European market in October, 2008. As a consequence, several pharmaceutical companies announced the interruption of their clinical research on

CB₁ receptor antagonists, including taranabant (from Merck) and otenabant (from Pfizer), both in Phase 3 of development. Some of the anxiogenic properties of rimonabant and analogs have been speculated to be due to their activity as inverse agonists; as a result, the therapeutic use of newly-developed neutral CB₁ antagonists has been proposed, with the hypothesis that these compounds would not elicit the untoward psychological effects observed with rimonabant and its analogs [180,181]; this idea is supported by recent findings, showing that unlike CB₁ receptor inverse agonists, the neutral antagonists of this targets fail to facilitate the acquisition or consolidation of fear [182].

CB₂ receptor ligands

Few studies have actually evaluated the role of CB₂ receptor in anxiety and stress response. While this receptor was posited to be mainly expressed mainly in immune cells and peripheral areas, its identification in the brain under pathological conditions, such as Alzheimer's disease, multiple sclerosis and amyotrophic lateral sclerosis spinal cord [183-185], led to a number of studies aimed at the assessment of its potential role in brain function and behavioral regulation. Some of these investigations indicated that the suppression of CB₂ receptor in the brain, through intracerebroventricular injection of antisense nucleotide sequences, elicited anxiolytic effects in rodents [186]. In contrast, Garcia-Gutierrez and Manzanares [187] recently described that the overexpression of CB₂ receptors reduced anxiogenic-related behaviors in the light-dark box and elevated plus maze. These premises point to the possibility that CB₂ receptor ligands may also play a role in the modulation of anxiety disorders. This hypothesis, however, awaits further examination with proper pharmacological tools.

CBD

Several studies suggest that THC and CBD may exert opposite actions on brain function and psychopathology [188], possibly in relation to the action of CBD as a potent CB₁ receptor antagonist/inverse agonist [21] (see above). Several lines of preclinical work have shown that CBD reduces the effects of THC on several behavioral functions [189-191]. In line with these data, CBD has been found to reduce the anxiety and improve the sensation of well being induced by an acute, high THC dose in healthy volunteers [192].

In contrast with these data, a number of studies have shown that CBD pretreatment potentiated the behavioral effects induced by THC [193-195]. These actions may signify the ability of CBD to inhibit cytochrome P450-mediated drug metabolism [196,197], which may increase THC blood and brain concentrations [193,195].

Notably, the behavioral outcomes of CBD do not appear to be only due to potential pharmacodynamic/pharmacokinetic competition with THC; indeed, recent studies have shown that CBD exerts inherent anxiolytic effects, both in rodent models [157,198-201] and, more recently, in patients affected by social phobia [202,203]. The anxiolytic action of CBD may be linked to 5-HT_{1A} receptor, but not through benzodiazepine receptors [204]. Of note, the anxiolytic action of CBD also appears to be bidirectional, as only low to moderate doses, but not high doses, have been associated with exert anxiolytic effects [200,205].

The anxiolytic action of CBD do not appear to be mediated by benzodiazepine receptors [204], but rather by 5-HT_{1A} serotonin receptors in the bed nucleus of the stria terminalis [206], a critical component of the amygdaloid complex involved in the regulation of stress response.

Accordingly, CBD has been shown to reduce amygdalar responses to fearful stimuli [207]; this mechanism may be essential for the anxiolytic effects of this compound in social phobia [203]. Furthermore, CBD has been shown to elicit antipanic effects through the activation of

5-HT_{1A} receptors in the dorsal periaqueductal gray, a critical area for the modulation of emotional reactivity to stress [208,209].

Endocannabinoid transport blockers

The systemic administration of the endocannabinoid transport blocker AM404 (Fig. 4) was shown to elicit anxiolytic-like behaviors in the elevated plus maze and defensive withdrawal in adult rats, as well as an attenuation of ultrasonic vocalizations in rat pups [175]. The same compound was shown to attenuate marble burying (a paradigm for compulsivity testing) in mice, suggesting that this compound may have some potential efficacy for OCD [206]. Interestingly, the anxiolytic effects of AM404 were shown to be contributed by both CB₁ and 5-HT_{1A} receptors [152,210], in a fashion similar to the potent CB₁ receptor agonist CP 55,940 [160]. Additionally, AM404 has been suggested to act as a FAAH inhibitor [211], although evidence in this respect is controversial [72]. Indeed, despite the identification of potential candidate endocannabinoid binding sites [212], no final evidence is currently available on the existence and/or molecular identity of the endocannabinoid transporter.

Although the possibility of targeting the endocannabinoid carrier for the development of anxiolytic compounds is appealing and has been targeted by a patent proposing these compounds as a pharmacological support for psychotherapy [213], the elusive molecular identity of the transporter itself has greatly limited the studies. Furthermore, preliminary data indicate that AM404 elicits reward in animals and is self-administered by squirrel monkeys [175,214], raising the possibility that endocannabinoid transport blockers may be addictive.

FAAH inhibitors

The prototypical FAAH inhibitor URB597 (Fig. 4) has been shown to reduce anxiety-like behaviors in rats, in a rimonabant-sensitive fashion [155,163,215-217]. In addition to its anxiolytic-like properties, URB597 was found to exert also antidepressant-like effects in several animal models with high face and predictive validity, such as the forced swim, tail suspension and chronic mild stress paradigms [89,210,216,218]. The anxiolytic action of FAAH inhibitors has been suggested to depend on the enhancement of anandamide in the dorsolateral periaqueductal gray [219]; interestingly, however, only low doses of URB597 in the prefrontal cortex were found to elicit anxiolytic-like effects, through CB₁ receptor activation. However, higher doses ceased to elicit anxiolysis, in view of their interaction with TP_{1V} vanilloid receptors [220]. Furthermore, the anxiolytic and antidepressant actions of FAAH inhibitors were observed only under conditions of high environmental aversiveness, but not under normal conditions [163,218,221]. Importantly, the psychotropic effects of FAAH inhibitors are partially distinct from those associated with cannabinoids, in that they appear to fail to reproduce the hedonic and interoceptive states produced by CB receptor agonists [89] and to induce self-administration in squirrel monkeys [222]. Taken together, these data suggest that FAAH inhibitors may be promising tools in the therapy of anxiety and mood disorders with a safer profile than cannabinoid direct agonists. This idea has been recently endorsed by several authors in recent articles and patents, featuring novel categories of highly selective and potent FAAH inhibitors [223-225] [226]. However, it should be noted that recent data have recently shown that URB597 induce a number of side effects in rats, including social withdrawal, working memory deficits [227] and impairments in auditory discrimination and reversal of olfactory discrimination [228].

MAGL inhibitors

The role of 2-AG in emotional regulation has been difficult to ascertain until the recent development of highly selective monoacylglycerol lipase (MAGL) inhibitors [35,223]. Several lines of evidence have suggested that 2-AG plays a pivotal role in the

pathophysiology of anxiety and defensive behaviors. The prototypical MAGL inhibitor, JZL184 (Fig. 4), has been shown to enhance the levels of 2-AG, but not anandamide; this effect is due to its extremely high selectivity for MAGL over FAAH and other brain serine hydrolases. Recent evidence has shown that this compound exerts anxiolytic-like effects in the elevated plus maze and in marble burying, at doses that do not affect locomotor activity [93,229,230]. Similarly to the effects described for FAAH inhibitors (see above), the anxiolytic effects of this compound were observed in highly aversive (or anxiogenic) contextual settings [229]. The neurobiological role of 2-AG in anxiety is still poorly understood, although several studies have shown that environmental stressors alter its biosynthesis and degradation in key brain structures controlling emotional regulation, including periaqueductal grey, amygdala and hippocampus [231,232]. Interestingly, recent evidence has shown that the anxiolytic properties of JZL184 appear to be mediated by CB₂, rather than CB₁ receptors [93], pointing to a potential implication of this receptor in the role of 2-AG in anxiety regulation.

CURRENT AND FUTURE DEVELOPMENTS

In light of the limitations of our current pharmacological armamentarium for anxiety disorders, the ability of cannabinoids to modulate emotional responses is extremely attractive for the development of novel anxiolytic agents [217]. At the same time, great concern arises from the protean role of cannabinoids on the regulation of these responses, as well as their misuse liability and other side effects. The identification of operational strategies for the employment of cannabinoids in the therapy of anxiety disorders is therefore a fundamental goal in psychiatry research.

As outlined above, clinical evidence strongly suggests that acute administration of low doses of CB₁ receptor agonists results in anxiolytic effects, while excessive activation of these targets elicits opposite outcomes, following a reverse U-shaped dose-response pattern. Hence, a primary strategy to harness the anxiolytic properties of cannabinoids could consist in the employment of partial, low-affinity CB₁ agonists, which may ensure a relatively high therapeutic index and the stabilization of the activation of this target within a range associated with mood enhancement and/or anxiolysis. This idea is indirectly supported by the mirroring observation that anecdotal reports on highly potent, high-affinity synthetic cannabinoids (such as those contained in “Spice” blends) trigger greater psychoactive effects than the partial CB agonist THC [26]. This concept indicates a potential evolution in the search for direct CB agonists, in sharp contrast with the previous trend aimed at the identification of high-affinity CB receptor activators.

An alternative strategy to achieve a similar therapeutic goal may lie in the combination of CB₁ receptor agonists with low dosages of antagonists (preferably neutral, in order to avoid potential side effects linked to CB₁ inverse agonism); this intriguing approach, which has been indicated in a recent patent [233], is based on the likely mechanism of action of Sativex®, a cannabinoid mouth spray containing THC and CBD (in a ratio of 1.08:1) and marketed for the treatment of neuropathic pain, spasticity and overactive bladder, in consideration of the action of CBD as a CB₁ receptor antagonist. However, recent preliminary clinical studies have shown that this formulation did not significantly reduce anxiety (in fact, it was reported to induce a mild, yet not significant increase of this symptom) [234,235], and that CBD did not appear to elicit a significant opposition to the effect of dronabinol [235], plausibly indicating that a higher concentration of this ingredient (or lower relative amount of THC) may be necessary to elicit anxiolytic effects.

A third, highly promising avenue for the development of cannabinoid-based anxiolytic therapies may be afforded by FAAH inhibitors. Unlike endocannabinoid transport blockers

and direct CB receptor agonists, these compounds exhibit a number of highly desirable properties for anxiolytic agents: first, they appear to maintain their anxiolytic and antidepressant effect not only under conditions of acute administration, but also following long-term treatment [93,210]; second, they appear to elicit their effects only in conditions of highly aversive environmental circumstances (i.e., similar to those that would in fact require an anxiolytic treatment); third, they have no apparent addiction liability [89,222]. The neurobiological bases of this phenomenon are not completely understood, and may be related to the involvement of other FAAH substrates, such as OEA or PEA; however, recent investigations suggest that the lack of 2-AG enhancement ensuing FAAH inactivation may contribute to the lack of reinforcing properties of URB597 [236], potentially suggesting a different role of anandamide and 2-AG in the modulation of reward; this idea is actually consistent with the recent finding that 2-AG induces self-administration in monkeys [237].

A key problem concerning the potential application of cannabinoid-related agents and cannabinoids is the relatively little information about their long-term effects following chronic administration. Indeed, the subjective effects of cannabis have been shown to be typically different in chronic users as compared to occasional marijuana smokers [238,239]. Prolonged consumption of cannabis has been shown to induce affective sequelae, including alexithymia and avolition [113,240-242]. Interestingly, tolerance has been shown to the effects of THC [243,244], while no information is available on endocannabinoid-related agents. Long-term administration of cannabinoids has been shown to result in a number of neuroplastic adaptive processes, including CB receptor down-regulation [245,246]. Some of these phenomena may indeed be critical in shaping the different emotional responsiveness to cannabis throughout life and reflect a potential pathophysiological loop which may compound the severity of pre-existing anxiety and affective disorders.

Finally, another important step for the employment of cannabinoid-based anxiolytic therapies will be the analysis of the vulnerability factors implicated in the differential responses and long-term sequelae induced by cannabis consumption. For example, numerous meta-analyses and longitudinal studies have established that cannabis consumption in adolescence is conducive to an increased risk for psychotic disorders [247-250]. This association is particularly significant in the presence of other genetic factors, such as the Val¹⁰⁸Met allelic variant of the gene encoding Catechol-O-methyltransferase (COMT) [251,252], one of the main enzymes for the degradation of the neurotransmitter dopamine. Interestingly, it has been shown that the synergistic effect of COMT haplotype and cannabis in adolescence is more robust in conjunction with predisposing environmental variables, such as the exposure to urbanicity and psychosocial stress [253]. Another gene that may modulate the behavioral responsiveness to cannabinoids is *Nrg1*, which encodes for the synaptic protein neuregulin 1. Indeed, the heterozygous deletion of this gene ablates the development of tolerance to the anxiogenic effects of CB receptor agonists [254,255]. These findings suggest that the employment of a pharmacogenetic approach may be a critical screening instrument to identify which patients may be treated with cannabis for medical purposes without risks of neuropsychiatric side effects. Notably, the role of genes in the mental sequelae of cannabis may also be contributed by epigenetic factors, in consideration of the recent finding that THC induces expression of histone deacetylase 3 [256].

While studies on the biological determinants of different responses to cannabis are still at their preliminary stages, advances in this area may be essential to allow a personalized approach for the employment of cannabinoid-based therapies in anxiety and mood disorders.

Acknowledgments

The present work was supported by the National Institute of Health grant R21HD070611 and the USC Zumberge Individual Research Grant (to MB).

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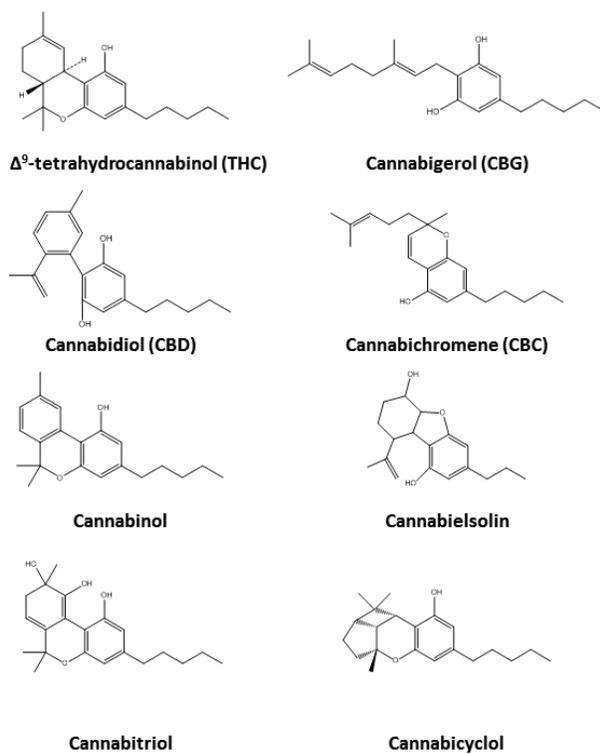


Fig. 1. Chemical structures of the major phytocannabinoids. For more details, see text.

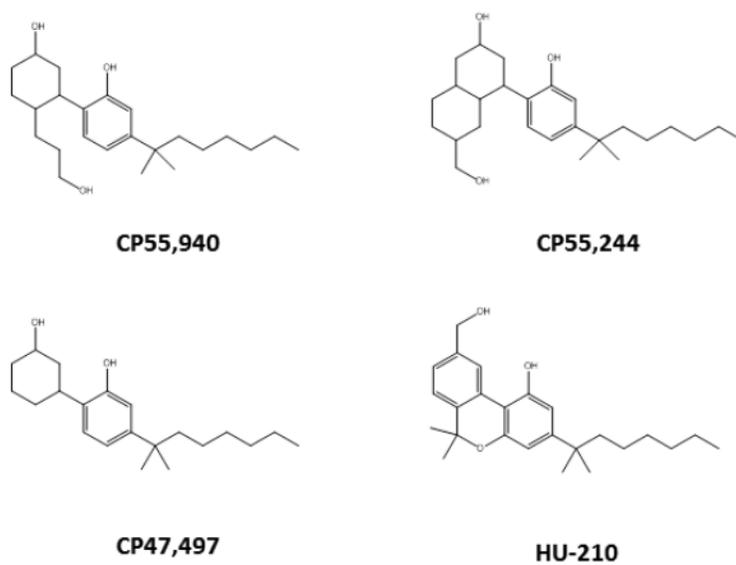


Fig. 2. Chemical structures of the synthetic THC analogs CP55,940, CP55,244, CP 47,497 and HU-210. For more details, see text.

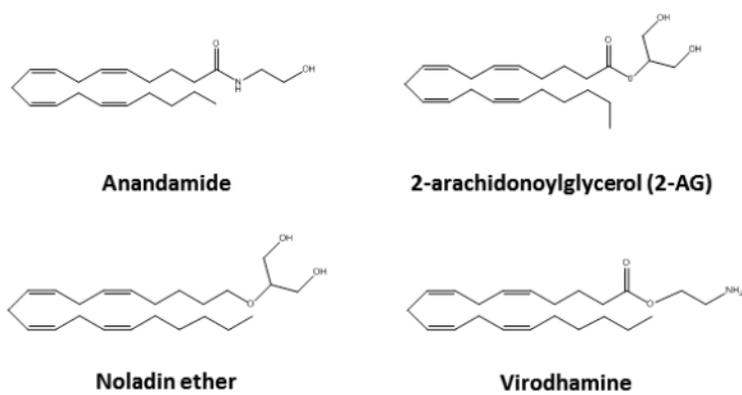


Fig. 3. Chemical structures of the major endocannabinoids. For more details, see text.

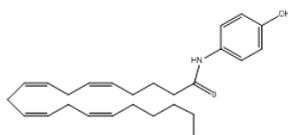
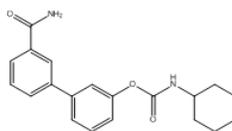
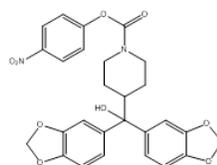
**AM404****URB597****JZL184**

Fig. 4. Chemical structures of endocannabinoid degradation inactivators. For more details, see text.

Table 1
Current pharmacological strategies for the treatment of anxiety disorders

1	Generalized anxiety disorder
a.	Benzodiazepines
b.	Buspirone
c.	Selective serotonin reuptake inhibitors
2	Panic attack
a.	High-potency benzodiazepines
b.	Tricyclic antidepressants
c.	Selective serotonin reuptake inhibitors
d.	Monoamine oxidase inhibitors
3	Post-traumatic stress disorder
a.	Selective serotonin reuptake inhibitors
b.	Low-dose antipsychotic agents
4	Obsessive-compulsive disorder
a.	Tricyclic antidepressants
b.	Selective serotonin reuptake inhibitors

Table 2
Paradigms for testing of anxiety-like behaviors in rodents

1	Unconditioned anxiety
	a. Tests for social anxiety
	i. Maternal separation-induced ultrasonic vocalizations (for pups)
	ii. Social interaction
	b. Tests based on approach/avoidance conflict
	i. Novel open field
	ii. Defensive withdrawal
	iii. Elevated plus maze
	iv. Elevated T-maze
	v. Zero maze
	vi. Light/dark box
	vii. Emergence test
	c. Tests based on antipredator defensive behavior
	i. Mouse defense test battery
	ii. Predator urine exposure test
	iii. Predator exposure test
	d. Other tests
	i. Novelty-induced feeding suppression
	ii. Marble burying
	iii. Defensive burying
2	Conditioned anxiety
	a. Tests on conditional fear
	i. Fear- conditioned freezing
	ii. Fear-potentiated startle
	iii. Conditional fear-induced analgesia
	b. Operant conflict test
	i. Geiller-Seifter test (conditioned suppression of eating)
	ii. Vogel test (conditioned suppression of drinking)

Cannabidiol as a Potential Treatment for Anxiety Disorders

Esther M. Blessing¹ · Maria M. Steenkamp¹ · Jorge Manzanares^{1,2} · Charles R. Marmar¹

Published online: 4 September 2015

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Abstract Cannabidiol (CBD), a *Cannabis sativa* constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

Keywords Cannabidiol · Endocannabinoids · Anxiety · Generalized anxiety disorder · Post-traumatic stress disorder

✉ Esther M. Blessing
esther.blessing@nyumc.org

¹ New York University School of Medicine, New York, NY, USA

² Instituto de Neurociencias de Alicante, Universidad Miguel Hernández and Consejo Superior de Investigaciones Científicas, Alicante, Spain

Introduction

Fear and anxiety are adaptive responses essential to coping with threats to survival. Yet excessive or persistent fear may be maladaptive, leading to disability. Symptoms arising from excessive fear and anxiety occur in a number of neuropsychiatric disorders, including generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), and obsessive–compulsive disorder (OCD). Notably, PTSD and OCD are no longer classified as anxiety disorders in the recent revision of the Diagnostic and Statistical Manual of Mental Disorders-5; however, excessive anxiety is central to the symptomatology of both disorders. These anxiety-related disorders are associated with a diminished sense of well-being, elevated rates of unemployment and relationship breakdown, and elevated suicide risk [1–3]. Together, they have a lifetime prevalence in the USA of 29 % [4], the highest of any mental disorder, and constitute an immense social and economic burden [5, 6].

Currently available pharmacological treatments include serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressant drugs, and partial 5-hydroxytryptamine (5-HT)_{1A} receptor agonists. Anticonvulsants and atypical antipsychotics are also used to treat PTSD. These medications are associated with limited response rates and residual symptoms, particularly in PTSD, and adverse effects may also limit tolerability and adherence [7–10]. The substantial burden of anxiety-related disorders and the limitations of current treatments place a high priority on developing novel pharmaceutical treatments.

Cannabidiol (CBD) is a phytocannabinoid constituent of *Cannabis sativa* that lacks the psychoactive effects of Δ^9 -tetrahydrocannabinol (THC). CBD has broad therapeutic properties across a range of neuropsychiatric disorders, stemming from diverse central nervous system actions [11, 12]. In recent

years, CBD has attracted increasing interest as a potential anxiolytic treatment [13–15]. The purpose of this review is to assess evidence from current preclinical, clinical, and epidemiological studies pertaining to the potential risks and benefits of CBD as a treatment for anxiety disorders.

Methods

A search of MEDLINE (PubMed), PsycINFO, Web of Science Scopus, and the Cochrane Library databases was conducted for English-language papers published up to 1 January 2015, using the search terms “cannabidiol” and “anxiety” or “fear” or “stress” or “anxiety disorder” or “generalized anxiety disorder” or “social anxiety disorder” or “social phobia” or “post-traumatic stress disorder” or “panic disorder” or “obsessive compulsive disorder”. In total, 49 primary preclinical, clinical, or epidemiological studies were included. Neuroimaging studies that documented results from anxiety-related tasks, or resting neural activity, were included. Epidemiological or clinical studies that assessed CBD’s effects on anxiety symptoms, or the potential protective effects of CBD on anxiety symptoms induced by cannabis use (where the CBD content of cannabis is inferred via a higher CBD:THC ratio), were included.

CBD Pharmacology Relevant to Anxiety

General Pharmacology and Therapeutic Profile

Cannabis sativa, a species of the *Cannabis* genus of flowering plants, is one of the most frequently used illicit recreational substances in Western culture. The 2 major phyto-cannabinoid constituents with central nervous system activity are THC, responsible for the euphoric and mind-altering effects, and CBD, which lacks these psychoactive effects. Preclinical and clinical studies show CBD possesses a wide range of therapeutic properties, including antipsychotic, analgesic, neuroprotective, anti-convulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties (see [11, 12, 16–19] for reviews). A review of potential side effects in humans found that CBD was well tolerated across a wide dose range, up to 1500 mg/day (orally), with no reported psychomotor slowing, negative mood effects, or vital sign abnormalities noted [20].

CBD has a broad pharmacological profile, including interactions with several receptors known to regulate fear and anxiety-related behaviors, specifically the cannabinoid type 1 receptor (CB₁R), the serotonin 5-HT_{1A} receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor [11, 12, 19, 21]. In addition, CBD may also regulate, directly or indirectly, the peroxisome proliferator-activated receptor- γ , the orphan G-protein-coupled receptor 55, the equilibrative nucleoside transporter, the adenosine transporter,

additional TRP channels, and glycine receptors [11, 12, 19, 21]. In the current review of primary studies, the following receptor-specific actions were found to have been investigated as potential mediators of CBD’s anxiolytic action: CB₁R, TRPV1 receptors, and 5-HT_{1A} receptors. Pharmacology relevant to these actions is detailed below.

The Endocannabinoid System

Following cloning of the endogenous receptor for THC, namely the CB₁R, endogenous CB₁R ligands, or “endocannabinoids” (eCBs) were discovered, namely anandamide (AEA) and 2-arachidonoylglycerol (reviewed in [22]). The CB₁R is an inhibitory G_{i/o} protein-coupled receptor that is mainly localized to nerve terminals, and is expressed on both γ -aminobutyric acid-ergic and glutamatergic neurons. eCBs are fatty acid derivatives that are synthesized on demand in response to neuronal depolarization and Ca²⁺ influx, via cleavage of membrane phospholipids. The primary mechanism by which eCBs regulate synaptic function is retrograde signaling, wherein eCBs produced by depolarization of the postsynaptic neuron activate presynaptic CB₁Rs, leading to inhibition of neurotransmitter release [23]. The “eCB system” includes AEA and 2-arachidonoylglycerol; their respective degradative enzymes fatty acid amide hydroxylase (FAAH) and monoacylglycerol lipase; the CB₁R and related CB₂ receptor (the latter expressed mainly in the periphery); as well as several other receptors activated by eCBs, including the TRPV1 receptor, peroxisome proliferator-activated receptor- γ , and G protein-coupled 55 receptor, which functionally interact with CB₁R signaling (reviewed in [21, 24]). Interactions with the TRPV1 receptor, in particular, appear to be critical in regulating the extent to which eCB release leads to inhibition or facilitation of presynaptic neurotransmitter release [25]. The TRPV1 receptor is a postsynaptic cation channel that underlies sensation of noxious heat in the periphery, with capsaicin (hot chili) as an exogenous ligand. TRPV1 receptors are also expressed in the brain, including the amygdala, periaqueductal grey, hippocampus, and other areas [26, 27].

The eCB system regulates diverse physiological functions, including caloric energy balance and immune function [28]. The eCB system is also integral to regulation of emotional behavior, being essential to forms of synaptic plasticity that determine learning and response to emotionally salient, particularly highly aversive events [29, 30]. Activation of CB₁Rs produces anxiolytic effects in various models of unconditioned fear, relevant to multiple anxiety disorder symptom domains (reviewed in [30–33]). Regarding conditioned fear, the effect of CB₁R activation is complex: CB₁R activation may enhance or reduce fear expression, depending on brain locus and the eCB ligand [34]; however, CB₁R activation potentially enhances fear extinction [35], and can prevent fear reconsolidation. Genetic manipulations that impede

CB₁R activation are anxiogenic [35], and individuals with eCB system gene polymorphisms that reduce eCB tone—for example, FAAH gene polymorphisms—exhibit physiological, psychological, and neuroimaging features consistent with impaired fear regulation [36]. Reduction of AEA–CB₁R signaling in the amygdala mediates the anxiogenic effects of corticotropin-releasing hormone [37], and CB₁R activation is essential to negative feedback of the neuroendocrine stress response, and protects against the adverse effects of chronic stress [38, 39]. Finally, chronic stress impairs eCB signaling in the hippocampus and amygdala, leading to anxiety [40, 41], and people with PTSD show elevated CB₁R availability and reduced peripheral AEA, suggestive of reduced eCB tone [42].

Accordingly, CB₁R activation has been suggested as a target for anxiolytic drug development [15, 43, 44]. Proposed agents for enhancing CB₁R activation include THC, which is a potent and direct agonist; synthetic CB₁R agonists; FAAH inhibitors and other agents that increase eCB availability, as well as nonpsychoactive cannabis phytocannabinoids, including CBD. While CBD has low affinity for the CB₁R, it functions as an indirect agonist, potentially via augmentation of CB₁R constitutional activity, or via increasing AEA through FAAH inhibition (reviewed in [21]).

Several complexities of the eCB system may impact upon the potential of CBD and other CB₁R-activating agents to serve as anxiolytic drugs. First, CB₁R agonists, including THC and AEA, have a biphasic effect: low doses are anxiolytic, but higher doses are ineffective or anxiogenic, in both preclinical models in and humans (reviewed in [33, 45]). This biphasic profile may stem from the capacity of CB₁R agonists to also activate TRPV1 receptors when administered at a high, but not low dose, as demonstrated for AEA [46]. Activation of TRPV1 receptors is predominantly anxiogenic, and thus a critical balance of eCB levels, determining CB₁ *versus* TRPV1 activation, is proposed to govern emotional behavior [27, 47]. CBD acts as a TRPV1 agonist at high concentrations, potentially by interfering with AEA inactivation [48]. In addition to dose-dependent activation of TRPV1 channels, the anxiogenic *versus* anxiolytic balance of CB₁R agonists also depends on dynamic factors, including environmental stressors [33, 49].

5-HT_{1A} Receptors

The 5-HT_{1A} receptor (5-HT_{1A}R) is an established anxiolytic target. Buspirone and other 5-HT_{1A}R agonists are approved for the treatment of GAD, with fair response rates [50]. In preclinical studies, 5-HT_{1A}R agonists are anxiolytic in animal models of general anxiety [51], prevent the adverse effects of stress [52], and enhance fear extinction [53]. Both pre- and postsynaptic 5-HT_{1A}Rs are coupled to various members of the G_{i/o} protein family. They are expressed on serotonergic neurons in the raphe, where they exert autoinhibitory function, and

various other brain areas involved in fear and anxiety [54, 55]. Mechanisms underlying the anxiolytic effects of 5-HT_{1A}R activation are complex, varying between both brain region, and pre- *versus* postsynaptic locus, and are not fully established [56]. While in vitro studies suggest CBD acts as a direct 5-HT_{1A}R agonist [57], in vivo studies are more consistent with CBD acting as an allosteric modulator, or facilitator of 5-HT_{1A} signaling [58].

Preclinical Evaluations

Generalized Anxiety Models

Relevant studies in animal models are summarized in chronological order in Table 1. CBD has been studied in a wide range of animal models of general anxiety, including the elevated plus maze (EPM), the Vogel-conflict test (VCT), and the elevated T maze (ETM). See Table 1 for the anxiolytic effect specific to each paradigm. Initial studies of CBD in these models showed conflicting results: high (100 mg/kg) doses were ineffective, while low (10 mg/kg) doses were anxiolytic [59, 60]. When tested over a wide range of doses in further studies, the anxiolytic effects of CBD presented a bell-shaped dose–response curve, with anxiolytic effects observed at moderate but not higher doses [61, 90]. All further studies of acute systemic CBD without prior stress showed anxiolytic effects or no effect [62, 65], the latter study involving intracerebroventricular rather than the intraperitoneal route. No anxiogenic effects of acute systemic CBD dosing in models of general anxiety have yet been reported. As yet, few studies have examined chronic dosing effects of CBD in models of generalized anxiety. Campos et al. [66] showed that in rat, CBD treatment for 21 days attenuated inhibitory avoidance acquisition [83]. Long et al. [69] showed that, in mouse, CBD produced moderate anxiolytic effects in some paradigms, with no effects in others.

Anxiolytic effects of CBD in models of generalized anxiety have been linked to specific receptor mechanisms and brain regions. The midbrain dorsal periaqueductal gray (DPAG) is integral to anxiety, orchestrating autonomic and behavioral responses to threat [91], and DPAG stimulation in humans produces feelings of intense distress and dread [92]. Microinjection of CBD into the DPAG produced anxiolytic effects in the EPM, VGC, and ETM that were partially mediated by activation of 5-HT_{1A}Rs but not by CB₁Rs [65, 68]. The bed nucleus of the stria terminalis (BNST) serves as a principal output structure of the amygdaloid complex to coordinate sustained fear responses, relevant to anxiety [93]. Anxiolytic effects of CBD in the EPM and VCT occurred upon microinjection into the BNST, where they depended on 5-HT_{1A}R

Table 1 Preclinical studies

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Silveira Filho et al. [59]	WR	i.p.	100 mg/kg , acute	GSCT	No effect	NA
Zuardi et al. [60]	WR	i.p.	10 mg/kg , acute	CER	Anxiolytic	NA
Onaivi et al. [61]	ICR mice	i.p.	0.01, 0.10, 0.50 , 1.00 , 2.50 , 5.00 , 10.00 , 50.00 , 100.00 mg/kg, acute	EPM	Anxiolytic	Effects ↓ by IP flumazenil, unchanged by naloxone
Guimaraes et al. [61]	WR	i.p.	2.5 , 5.0 , 10.0 and 20.0 mg/kg, acute	EPM	Anxiolytic	NA
Moreira et al. [62]	WR	i.p.	2.5, 5.0 and 10.0 mg/kg, acute	VCT	Anxiolytic	Effect unchanged by IP flumazenil
Ressel et al. [63]	WR	i.p.	10 mg/kg, acute	CFC	Anxiolytic	NA
Campos et al. [64]	WR	dIPAG	15.0, 30.0 , 60.0 nmol/0.2 µl, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra-dIPAG WAY100635 but not intra-dIPAG AM251
Bitencourt et al. [65]	WR	i.c.v.	2.0 µg/µl 5 min before extinction, acute	CFC extinction EPM before and 24 h after CFC	Anxiolytic No effect before CFC Anxiolytic following CFC	Extinction effect ↓ by SR141716A but not capsazepine
Campos et al. [66]	WR	dIPAG	30 , 60 mg/kg, acute	EPM	Anxiolytic	Intra-dIPAG capsazepine renders 60 mg/kg anxiolytic
Ressel et al. [67]	WR	i.p.	1, 10 or 20 mg/kg, acute	RS	Anxiolytic, ↓ Pressor ↓ Tachycardia Anxiolytic	All effects ↓ by systemic WAY100635
Soares et al. [68]	WR	dIPAG	15, 30 or 60 nmol, acute	EPM 24 h following RS ETM	Anxiolytic Panicolytic Panicolytic	All effects ↓ by intra-dIPAG WAY100635 but not AM251
Long et al. [69]	C57BL/6 J mice	i.p.	1, 5, 10, 50 mg/kg, chronic, daily/21 d	PAG E-stim EPM L-DT	No effect 1 mg/kg anxiolytic No effect	NA
Lemos et al. [70]	WR	i.p. PL IL	10 mg/kg IP, 30 nmol intra-PL and intra-IL, acute	SI OF CFC	50 mg/kg anxiolytic IP and PL anxiolytic IL angiogenic	NA
Casarotto et al. [71]	C57BL/6 J mice	i.p.	15, 30 , and 60 mg/kg, acute, or subchronic, daily/7 d	MBT	Anticompulsive	Effect ↓ by IP/AM251 but not WAY100635
Gomes et al. [72]	WR	BNST	15, 30 , and 60 nmol, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra BNST WAY100635
Granjeiro et al. [73]	WR	Intracisternal	15, 30 , and 60 nmol, acute	RS EPM 24 h after RS	Anxiolytic, ↓ Pressor Anxiolytic	NA
Deiana et al. [74]	SM	i.p. Oral	120 mg/kg, acute	MBT	Anticompulsive	NA
Uribe-Marino et al. [75]	SM	i.p.	0.3, 3.0 , 30.0 mg/kg, acute	PS	Panicolytic	NA

Table 1 (continued)

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Stern et al. [76]	WR	i.p.	3, 10, 30 mg/kg immediately after retrieval, acute	Reconsolidation blockade	Anxiolytic 1 and 7 d old fear memories disrupted	Effect ↓ by AM251 but not WAY100635
Campos et al. [77]	WR	i.p.	5 mg/kg , subchronic, daily/7 d	EPM following PS	Anxiolytic	Effects ↓ by IP WAY100635
Hsiao et al. [78]	WR	CeA	1 μg/μl	REM sleep time EPM	↓ REM sleep suppression Anxiolytic	NA
Gomes et al. [79]	WR	BNST	15, 30, 60 nmol , acute	OF CFC	Anxiolytic Anxiolytic	Both effects ↓ by intra-BNST WAY100635
El Batsch et al. [80]	LE-HR	i.p.	10 mg/kg , chronic, daily/14 d	CFC	Anxiogenic	NA
Campos et al. [81]	C57BL/6 mice	i.p.	30 mg/kg 2 h after CUS, chronic daily/14 d	EPM NSF	Anxiolytic Anxiolytic	Both effects ↓ by AM251
Do Monte et al. [82]	L-E HR	IL	1 μg or 0.4 μg/0.2 μl 5 min before extinction daily/4 d	Extinction of CFC	Anxiolytic	Effect ↓ by IP rimonabant
Campos et al. [83]	Rat	i.p.	5 mg/kg , chronic, daily/21 d	ETM	Anxiolytic Panicolytic	Panicolytic effect ↓ by intra-dIPAG WAY100635
Almeida et al. [84]	Rat	i.p.	1, 5, 15 mg/kg , acute	SI	Anxiolytic	NA
Gomes et al. [85]	WR	BNST	30 and 60 nmol , acute	RS	Anxiogenic ↑ Tachycardia	Effect ↓ by WAY100635
Twardowschy et al. [86]	SM	i.p.	3 mg/kg , acute	PS	Panicolytic	Effects ↓ by IP WAY100635
Focagga et al. [87]	WR	PL	15, 30, 60 nmol , acute	EPM EPM after RS CFC	Anxiogenic Anxiolytic Anxiolytic	All effects ↓ by intra PL WAY100635 Anxiolytic EPM effect post-RS ↓ by IP metyrapone
Nardo et al. [88]	SM	i.p.	30 mg/kg , acute	MBT	Anticompulsive	NA
da Silva et al. [89]	WR	SNpr	5 μg/0.2 μl	GABA _A blockade in dISC	Panicolytic	Both effects ↓ by AM251

Effective doses are in bold

Receptor specific agents: AM251 = cannabinoid receptor type 1 (CB₁R) inverse agonist; WAY100635 = 5-hydroxytryptamine 1A antagonist; SR141716A = CB₁R antagonist; rimonabant = CB₁R antagonist; capsazepine = transient receptor potential vanilloid type 1 antagonist; naloxone = opioid antagonist; flumazenil = GABA_A receptor antagonist

Anxiolytic effects in models used: CER = reduced fear response; CFC = reduced conditioned freezing; CFC extinction = reduced freezing following extinction training; EPM = reduced % time in open arm; ETM = decreased inhibitory avoidance; L-DT = increased % time in light; VCT = increased licks indicating reduced conflict; NSF = reduced latency to feed; OF = increased % time in center; SI = increased social interaction

Anticompulsive effects: MBT = reduced burying

Panicolytic effects: ETM = decreased escape; GABA_A blockade in dISC = defensive immobility, and explosive escape; PAG-E-Stim = increased threshold for escape; PS = reduced explosive escape

WR = Wistar rats; SM = Swiss mice; L-E HR = Long-Evans hooded rats; i.p. = intraperitoneal; dIPAG = dorsolateral periaqueductal gray; i.c.v. = intracerebroventricular; PL = prelimbic; IL = infralimbic; BNST = bed nucleus of the stria terminalis; CeA = amygdala central nucleus; SNpr = substantia nigra pars reticularis; CUS = chronic unpredictable stress; GSCT = Geller-Seifter conflict test; CER = conditioned emotional response; EPM = elevated plus maze; VCT = Vogel conflict test; CFC = contextual fear conditioning; RS = restraint stress; ETM = elevated T maze; PAG E-stim = electrical stimulation of the dIPAG; L-DT = light-dark test; SI = social interaction; OF = open field; MBT = marble-burying test; PS = predator stress; NSF = novelty suppressed feeding test; GABA_A = γ-aminobutyric acid receptor A; dISC = deep layers superior colliculus; REM = rapid eye movement; NA = not applicable

activation [79], and also upon microinjection into the central nucleus of the amygdala [78]. In the prelimbic cortex, which drives expression of fear responses via connections with the amygdala [94], CBD had more complex effects: in unstressed rats, CBD was anxiogenic in the EPM, partially via 5-HT_{1A}R receptor activation; however, following acute restraint stress, CBD was anxiolytic [87]. Finally, the anxiolytic effects of systemic CBD partially depended on GABA_A receptor activation in the EPM model but not in the VCT model [61, 62].

As noted, CBD has been found to have a bell-shaped response curve, with higher doses being ineffective. This may reflect activation of TRPV1 receptors at higher dose, as blockade of TRPV1 receptors in the DPAG rendered a previously ineffective high dose of CBD as anxiolytic in the EPM [66]. Given TRPV1 receptors have anxiogenic effects, this may indicate that at higher doses, CBD's interaction with TRPV1 receptors to some extent impedes anxiolytic actions, although was notably not sufficient to produce anxiogenic effects.

Stress-induced Anxiety Models

Stress is an important contributor to anxiety disorders, and traumatic stress exposure is essential to the development of PTSD. Systemically administered CBD reduced acute increases in heart rate and blood pressure induced by restraint stress, as well as the delayed (24 h) anxiogenic effects of stress in the EPM, partially by 5-HT_{1A}R activation [67, 73]. However intra-BNST microinjection of CBD *augmented* stress-induced heart rate increase, also partially via 5-HT_{1A}R activation [85]. In a subchronic study, CBD administered daily 1 h after predator stress (a proposed model of PTSD) reduced the long-lasting anxiogenic effects of chronic predator stress, partially via 5-HT_{1A}R activation [77]. In a chronic study, systemic CBD prevented increased anxiety produced by chronic unpredictable stress, in addition to increasing hippocampal AEA; these anxiolytic effects depended upon CB₁R activation and hippocampal neurogenesis, as demonstrated by genetic ablation techniques [81]. Prior stress also appears to *modulate* CBD's anxiogenic effects: microinjection of CBD into the prelimbic cortex of unstressed animals was anxiogenic in the EPM but following restraint stress was found to be anxiolytic [87]. Likewise, systemic CBD was anxiolytic in the EPM following but not prior to stress [65].

PD and Compulsive Behavior Models

CBD inhibited escape responses in the ETM and increased DPAG escape electrical threshold [68], both proposed models of panic attacks [95]. These effects partially depended on 5-HT_{1A}R activation but were not affected by CB₁R blockade. CBD was also panicolytic in the predator–prey model, which

assesses explosive escape and defensive immobility in response to a boa constrictor snake, also partially via 5-HT_{1A}R activation; however, more consistent with an anxiogenic effect, CBD was also noted to decrease time spent outside the burrow and increase defensive attention (not shown in Table 1) [75, 86]. Finally, CBD, partially via CB₁Rs, decreased defensive immobility and explosive escape caused by bicuculline-induced neuronal activation in the superior colliculus [89]. Anticompulsive effects of CBD were investigated in marble-burying behavior, conceptualized to model OCD [96]. Acute systemic CBD reduced marble-burying behavior for up to 7 days, with no attenuation in effect up to high (120 mg/kg) doses, and effect shown to depend on CB₁Rs but not 5-HT_{1A}Rs [71, 74, 88].

Contextual Fear Conditioning, Fear Extinction, and Reconsolidation Blockade

Several studies assessed CBD using contextual fear conditioning. Briefly, this paradigm involves pairing a neutral context, the conditioned stimulus (CS), with an aversive unconditioned stimulus (US), a mild foot shock. After repeated pairings, the subject learns that the CS predicts the US, and subsequent CS presentation elicits freezing and other physiological responses. Systemic administration of CBD prior to CS re-exposure reduced conditioned cardiovascular responses [63], an effect reproduced by microinjection of CBD into the BNST, and partially mediated by 5-HT_{1A}R activation [79]. Similarly, CBD in the prelimbic cortex reduced conditioned freezing [70], an effect prevented by 5-HT_{1A}R blockade [87]. By contrast, CBD microinjection in the infralimbic cortex *enhanced* conditioned freezing [70]. Finally, El Batsh et al. [80] reported that repeated CBD doses over 21 days, that is chronic as opposed to acute treatment, *facilitated* conditioned freezing. In this study, CBD was administered prior to conditioning rather than prior to re-exposure as in acute studies, thus further directly comparable studies are required.

CBD has also been shown to enhance extinction of contextually conditioned fear responses. Extinction training involves repeated CS exposure in the absence of the US, leading to the formation of a new memory that inhibits fear responses and a decline in freezing over subsequent training sessions. Systemic CBD administration immediately before training markedly enhanced extinction, and this effect depended on CB₁R activation, without involvement of TRPV1 receptors [65]. Further studies showed CB₁Rs in the infralimbic cortex may be involved in this effect [82].

CBD also blocked reconsolidation of aversive memories in rat [76]. Briefly, fear memories, when reactivated by re-exposure (retrieval), enter into a labile state in

which the memory trace may either be reconsolidated or extinguished [97], and this process may be pharmacologically modulated to achieve reconsolidation blockade or extinction. When administered immediately following retrieval, CBD prevented freezing to the conditioned context upon further re-exposure, and no reinstatement or spontaneous recovery was observed over 3 weeks, consistent with reconsolidation blockade rather than extinction [76]. This effect depended on CB₁R activation but not 5-HT_{1A}R activation [76].

Summary and Clinical Relevance

Overall, existing preclinical evidence strongly supports the potential of CBD as a treatment for anxiety disorders. CBD exhibits a broad range of actions, relevant to multiple symptom domains, including anxiolytic, panicolytic, and anticomulsive actions, as well as a decrease in autonomic arousal, a decrease in conditioned fear expression, enhancement of fear extinction, reconsolidation blockade, and prevention of the long-term anxiogenic effects of stress. Activation of 5-HT_{1A}Rs appears to mediate anxiolytic and panicolytic effects, in addition to reducing conditioned fear expression, although CB₁R activation may play a limited role. By contrast, CB₁R activation appears to mediate CBD's anticomulsive effects, enhancement of fear extinction, reconsolidation blockade, and capacity to prevent the long-term anxiogenic consequences of stress, with involvement of hippocampal neurogenesis.

While CBD predominantly has acute anxiolytic effects, some species discrepancies are apparent. In addition, effects may be contingent on prior stress and vary according to brain region. A notable contrast between CBD and other agents that target the eCB system, including THC, direct CB₁R agonists and FAAH inhibitors, is a lack of anxiogenic effects at a higher dose. Further receptor-specific studies may elucidate the receptor specific basis of this distinct dose response profile. Further studies are also required to establish the efficacy of CBD when administered in chronic dosing, as relatively few relevant studies exist, with mixed results, including both anxiolytic and anxiogenic outcomes.

Overall, preclinical evidence supports systemic CBD as an acute treatment of GAD, SAD, PD, OCD, and PTSD, and suggests that CBD has the advantage of not producing anxiogenic effects at higher dose, as distinct from other agents that enhance CB₁R activation. In particular, results show potential for the treatment of multiple PTSD symptom domains, including reducing arousal and avoidance, preventing the long-term adverse effects of stress, as well as enhancing the extinction and blocking the reconsolidation of persistent fear memories.

Human Experimental and Clinical Studies

Evidence from Acute Psychological Studies

Relevant studies are summarized in Table 2. The anxiolytic effects of CBD in humans were first demonstrated in the context of reversing the anxiogenic effects of THC. CBD reduced THC-induced anxiety when administered simultaneously with this agent, but had no effect on baseline anxiety when administered alone [99, 100]. Further studies using higher doses supported a lack of anxiolytic effects at baseline [101, 107]. By contrast, CBD potently reduces experimentally induced anxiety or fear. CBD reduced anxiety associated with a simulated public speaking test in healthy subjects, and in subjects with SAD, showing a comparable efficacy to ipsapirone (a 5-HT_{1A}R agonist) or diazepam [98, 105]. CBD also reduced the presumed anticipatory anxiety associated with undergoing a single-photon emission computed tomography (SPECT) imaging procedure, in both healthy and SAD subjects [102, 104]. Finally, CBD enhanced extinction of fear memories in healthy volunteers: specifically, inhaled CBD administered prior to or after extinction training in a contextual fear conditioning paradigm led to a trend-level enhancement in the reduction of skin conductance response during reinstatement, and a significant reduction in expectancy (of shock) ratings during reinstatement [106].

Evidence from Neuroimaging Studies

Relevant studies are summarized in Table 3. In a SPECT study of resting cerebral blood flow (rCBF) in normal subjects, CBD reduced rCBF in left medial temporal areas, including the amygdala and hippocampus, as well as the hypothalamus and left posterior cingulate gyrus, but increased rCBF in the left parahippocampal gyrus. These rCBF changes were not correlated with anxiolytic effects [102]. In a SPECT study, by the same authors, in patients with SAD, CBD reduced rCBF in overlapping, but distinct, limbic and paralimbic areas; again, with no correlations to anxiolytic effects [104].

In a series of placebo-controlled studies involving 15 healthy volunteers, Fusar-Poli et al. investigated the effects of CBD and THC on task-related blood-oxygen-level dependent functional magnetic resonance imaging activation, specifically the go/no-go and fearful faces tasks [109, 110]. The go/no-go task measures response inhibition, and is associated with activation of medial prefrontal, dorsolateral prefrontal, and parietal areas [111]. Response activation is diminished in PTSD and other anxiety disorders, and increased activation predicts response to treatment [112]. CBD produced no changes in predicted areas (relative to placebo) but reduced activation in the left insula, superior temporal gyrus, and transverse temporal gyrus. The fearful faces task activates the amygdala, and other medial temporal areas involved in

Table 2 Human psychological studies

Study	Subjects, design	CBD route, dose	Measure	Effect
Karniol et al. [99]	HV, DBP	Oral, 15, 30, 60 mg, alone or with THC, acute, at 55, 95, 155, and 185 min	Anxiety and pulse rate after THC and at baseline	↓ THC-induced increases in subjective anxiety and pulse rate No effect at baseline
Zuardi et al., [100]	HV, DBP	Oral 1 mg/kg alone or with THC, acute, 80 min	STAI score after THC	↓ THC-induced increases in STAI scores
Zuardi et al. [98]	HV, DBP	Oral 300 mg, acute, 80 min	VAMS, STAI and BP following SPST	↓ STAI scores ↓ VAMS scores ↓ BP
Martin-Santos et al. [101]	HV, DBP	Oral 600 mg, acute, 1, 2, 3 h	Baseline anxiety and pulse rate	No effect
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	VAMS before SPECT	↓ VAMS scores
Bhattacharyya et al. [103]	15 HV, DBP	Oral 600 mg, acute, 1, 2, 3 h	SPECT STAI scores VAMS scores	↓ STAI scores ↓ VAMS scores
Crippa et al. [104]	SAD and HC, DBP	Oral 400 mg, acute, 75 and 140 min	VAMS before SPECT SPECT	↓ VAMS scores
Bergamaschi et al. [105]	SAD and HC, DBP	Oral 600 mg, acute, 1, 2, 3 h	VAMS, SSPS-N, cognitive impairment, SCR, HR after SPST	↓ VAMS, SSPS-N and cognitive impairment, no effect on SCR or HR
Das et al. [106]	HV, DBP	Inhaled, 32 mg, acute, immediately following, before, after extinction	SCR and shock expectancy following extinction	CBD after extinction training produced trend level reduction in SCR and decreased shock expectancy
Hindocha et al. [107]	Varying in schizotypy and cannabis use, DBP	Inhaled, 16 mg, acute	Baseline VAS anxiety	No significant effect of CBD

HV = healthy volunteers; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; THC = Δ^9 -tetrahydrocannabinol; STAI = Spielberger's state trait anxiety inventory; VAMS = visual analog mood scale; BP = blood pressure; SPST = simulated public speaking test; SCR = skin conductance response; SPECT = single-photon emission computed tomography; SSPS-N = negative self-evaluation subscale; HR = heart rate; VAS = visual analog scale, CBD = cannabidiol

Table 3 Neuroimaging studies

Study	Subjects, design	CBD route, dose, timing	Measure	Effect of CBD
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	SPECT, resting (rCBF)	↓ rCBF in left medial temporal cluster, including amygdala and HPC, also ↓ rCBF in the HYP and posterior cingulate gyrus ↑ rCBF in left PHG
Borgwardt et al. [108]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI during oddball and go/no-go task	↓ Activation in left insula, STG and MTG
Fusar-Poli et al. [109]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI activation during fearful faces task	↓ Activation in left medial temporal region, including amygdala and anterior PHG, and in right ACC and PCC
Fusar-Poli et al. [110]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI functional connectivity during fearful faces task	↓ Functional connectivity between L) AMY and ACC
Crippa et al. [104]	SAD and HC, DBP	Oral 400 mg, acute, 75 and 140 min	SPECT, resting (rCBF)	↓ rCBF in the left PHG, HPC and ITG. ↑ rCBF in the right posterior cingulate gyrus

CBD = cannabidiol; HV = healthy controls; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; SPECT = single-photon emission computed tomography; rCBF = regional cerebral blood flow; fMRI = functional magnetic resonance imaging; HPC = hippocampus; HYP = hypothalamus; PHG = parahippocampal gyrus; STG = superior temporal gyrus; MTG = medial temporal gyrus; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex

emotion processing, and heightened amygdala response activation has been reported in anxiety disorders, including GAD and PTSD [113, 114]. CBD attenuated blood-oxygen-level dependent activation in the left amygdala, and the anterior and posterior cingulate cortex in response to intensely fearful faces, and also reduced amplitude in skin conductance fluctuation, which was highly correlated with amygdala activation [109]. Dynamic causal modeling analysis in this data set further showed CBD reduced forward functional connectivity between the amygdala and anterior cingulate cortex [110].

Evidence from Epidemiological and Chronic Studies

Epidemiological studies of various neuropsychiatric disorders indicate that a higher CBD content in chronically consumed cannabis may protect against adverse effects of THC, including psychotic symptoms, drug cravings, memory loss, and hippocampal gray matter loss [115–118] (reviewed in [119]). As THC acutely induces anxiety, this pattern may also be evident for chronic anxiety symptoms. Two studies were identified, including an uncontrolled retrospective study in civilian patients with PTSD patients [120], and a case study in a patient with severe sexual abuse-related PTSD [121], which showed that chronic cannabis use significantly reduces PTSD symptoms; however, these studies did not include data on the THC:CBD ratio. Thus, overall, no outcome data are currently available regarding the chronic effects of CBD in the treatment of anxiety symptoms, nor do any data exist regarding the potential protective effects of CBD on anxiety potentially induced by chronic THC use.

Summary and Clinical Relevance

Evidence from human studies strongly supports the potential for CBD as a treatment for anxiety disorders: at oral doses ranging from 300 to 600 mg, CBD reduces experimentally induced anxiety in healthy controls, without affecting baseline anxiety levels, and reduces anxiety in patients with SAD. Limited results in healthy subjects also support the efficacy of CBD in acutely enhancing fear extinction, suggesting potential for the treatment of PTSD, or for enhancing cognitive behavioral therapy. Neuroimaging findings provide evidence of neurobiological targets that may underlie CBD's anxiolytic effects, including reduced amygdala activation and altered medial prefrontal amygdala connectivity, although current findings are limited by small sample sizes, and a lack of independent replication. Further studies are also required to establish whether chronic, in addition to acute CBD dosing is anxiolytic in human. Also, clinical findings are currently limited to SAD, whereas preclinical evidence suggests CBD's potential to treat multiple symptom domains relevant to GAD, PD, and, particularly, PTSD.

Conclusions

Preclinical evidence conclusively demonstrates CBD's efficacy in reducing anxiety behaviors relevant to multiple disorders, including PTSD, GAD, PD, OCD, and SAD, with a notable lack of anxiogenic effects. CBD's anxiolytic actions appear to depend upon CB₁Rs and 5-HT_{1A}Rs in several brain regions; however, investigation of additional receptor actions may reveal further mechanisms. Human experimental findings support preclinical findings, and also suggest a lack of anxiogenic effects, minimal sedative effects, and an excellent safety profile. Current preclinical and human findings mostly involve acute CBD dosing in healthy subjects, so further studies are required to establish whether chronic dosing of CBD has similar effects in relevant clinical populations. Overall, this review emphasizes the potential value and need for further study of CBD in the treatment of anxiety disorders.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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Cannabis in the Treatment of Dystonia, Dyskinesias, and Tics

Barbara S. Koppel¹ 

Published online: 14 August 2015

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Abstract Cannabis has been used for many medicinal purposes, including management of spasms, dystonia, and dyskinesias, with variable success. Its use for tetanus was described in the second century BCE, but the literature continues to include more case reports and surveys of its beneficial effects in managing symptoms of hyperkinetic movement disorders than randomized controlled trials, making evidence-based recommendations difficult. This paper reviews clinical research using various formulations of cannabis (botanical products, oral preparations containing Δ^9 -tetrahydrocannabinol and/or cannabidiol) and currently available preparations in the USA (nabilone and dronabinol). This has been expanded from a recent systematic review of cannabis use in several neurologic conditions to include case reports and case series and results of anonymous surveys of patients using cannabis outside of medical settings, with the original evidence classifications marked for those papers that followed research protocols. Despite overlap in some patients, dyskinesias will be treated separately from dystonia and chorea; benefit was not established beyond individual patients for these conditions. Tics, usually due to Tourettes, did respond to cannabis preparations. Side effects reported in the trials will be reviewed but those due to recreational use, including the dystonia that can be secondary to synthetic marijuana preparations, are outside the scope of this paper.

Keywords Cannabis · Marijuana · THC · Cannabidiol · Dystonia · Dyskinesias · Chorea · Tics

Introduction

Endocannabinoid receptors (CB₁R and CB₂R) are plentiful in the basal ganglia [1], implying they play a role in normal motor function and that pharmaceutical (or recreational) cannabis formulations, which are agonists at both sites, might alleviate symptoms of movement disorders. CB₁R are expressed in γ -aminobutyric acid (GABA)ergic neurons of the caudate and striatum, presynaptic terminals in the globus pallidus externa and interna, substantia nigra pars reticulata and pars compacta, and are present in glutamatergic projections to and from the cortex and the subthalamic nucleus. In addition to GABAergic and glutamatergic pathways, dopaminergic inputs are also influenced by endocannabinoids. In general, the cannabinoid signals would be upregulated if a disease was marked by hypokinesia, such as in Parkinson disease (PD), as the cannabinoid ligands act overall to suppress movement, and would be decreased in hyperkinetic movement disorders such as Huntington disease (HD). However, paradoxical responses can occur during degeneration as the receptors in various parts of the basal ganglia die (Table 1).

The complexity of feedback loops in this region, with indirect actions of the endocannabinoid system modulating other inhibitory, excitatory or dopaminergic transmission, partially explains this. In addition, in degenerative diseases such as HD and PD, progressive loss of specific structures, along with their endocannabinoid receptors occurs. The receptor loss will dampen any effects of CB_{1/2}R agonists such as Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD). Other endocannabinoid receptors, such as transient receptor potential vanilloid-type 1, may be successfully stimulated in early

✉ Barbara S. Koppel
Barbara.Koppel@nychhc.org

¹ New York Medical College, Metropolitan Hospital, 1901 First Ave. Suite 7C5, New York, NY 10029, USA

Table 1 Cannabis formulations used in various movement disorders

Generic name	Trade name	Use	Dosage and component(s)	Reference
PD				
Cannabis extract	Cannador Not stated	Dopa-induced dyskinesias/dystonia Tremor/dystonia dopa-induced dyskinesias	Δ^9 -THC 2.5 + CBD 1.25 100–600 mg/daily 0.03 mg/kg/daily 25mgTHC/kg//daily 75 mg/daily	[7, 10*, 16, 17*, 18*]
Rimonabant (CBD antagonist)	SR141716	Dopa-induced dyskinesias	Experimental	[20]
Inhaled botanical marijuana	–	Parkinson tremor and dyskinesias	1 cigarette 2.9 % THC Survey of unsupervised smoked marijuana 0.5gm/cig	[13*,14, 15, 19]
Nabilone	Cesamet	Levodopa-induced dyskinesias	Synthetic cannabinoid 0.03 mg/kg 0.03 mg/kg	[10*, 16]
Dystonia				
Dronabinol	Marinol	Cervical dystonia Dystonia and tics in MS	7.5 mg twice daily 2.5 mg twice daily	[5*, 11]
CBD or cannabis extract	None	Primary dystonias	10 mg/kg/day up to 75 mg/day 100 mg CBD	[7, 18*, 23]
Inhaled botanical marijuana		Spasms Hemidystonia (in Wilson disease)	Not stated 1 MJ Cigarette/dy 3–4 g/day	[6, 8, 9]
HD				
Nabilone	Cesamet	Motor score no improvement, some in chorea and NPI	1–2 mg/day	[23*†, 24*]
CBD or cannabis extract	None		10 mg/kg/day, mean 700 mg	[21*‡]
Tourette syndrome				
Botanical smoked marijuana			0.5–2.0 cigarettes/day One “cone”/night survey (self-prescribed)	[25–27]
THC capsule	None	Tics and vocalizations	2.5 mg Δ^9 -THC, maximum 10 mg/day	[28†, 29 ‡]

If no evidence classification is indicated, it means it was class IV. PD = Parkinson disease; Δ^9 -THC = Δ^9 -tetrahydrocannabinol (the principal psychoactive agent); CBD = cannabidiol (a lesspsychoactive resin extract constituent of the plant *Cannabis Sativa*); MS = multiple sclerosis; HD = Huntington disease; NPI = Neuropsychiatric index

*Class I

† Class II

‡ Class III

stages of HD, but medications do not exist yet to test this. In fact, CB₁R antagonists, similarly experimental at this stage, might be beneficial for hypokinetic symptoms such as hypokinesia in PD.

Contradictory and confusing efficacy has been reported when cannabis medications (or smoked phytocannabinoids) are used to treat movement disorder symptoms [2, 3]. Although the loss of receptors plays some role, more likely currently available cannabis preparations, which contain different amounts and combinations of cannabinoids (at least 60 have been described) with variable potency and psychoactive content (present in Δ^9 -THC but not CBD) with different, usually low, doses, make standardized comparisons impossible. Scoring methods, other than counting individual tics or choreiform movements, add to the researcher's difficulty in measuring

efficacy. The potency, especially Δ^9 -THC content, is kept deliberately low to limit side effects (or patient recognition in those experienced with marijuana), which contributes to treatment failure. Studies are small with problematic recruitment for a substance that will require limitation of activities such as driving, use of a stigmatized medication, and of short duration (sometimes single dose) to avoid abuse or addiction [4]. Even obtaining study drug status in the USA requires working with the various government agencies, and is only becoming easier in the face of a serious epidemic of opiate overuse and toxicity. The Drug Enforcement Agency continues to classify medical cannabis as a Schedule I drug (that with no therapeutic use).

Investigation into cannabis' medicinal use began with promising case reports and anonymous surveys, followed by limited clinical research often conducted outside the USA,

which has not proved sufficient to allow many evidence-based recommendations. Although overlap exists in individuals, in this review dyskinesias, dystonia, and chorea will be considered separately. Although tremor was studied in patients suffering from multiple sclerosis, there is no information on essential tremor. Tics will be considered separately, as the mechanism differs.

Dystonia

Dystonia involves overactivity of muscles required for normal movement, with extra force or activation of nearby but unnecessary muscles, including those that should be turned off to facilitate movement, and is often painful in addition to interfering with function. It can be primary, as in torticollis and blepharospasm/orofacial dyskinesias or dystonias (Meige syndrome) or as part of another condition such as HD and tardive dyskinesia after dopa-blocking drugs. The globus pallidus and substantia nigra pars reticularis contain CB₁R, with cannabinoids acting as neuromodulators and enhancing GABA release and reducing its reuptake [5].

In 1981, Marsden described improvement in a patient with torticollis who smoked cannabis [6]. An open-label series followed [7], and self-reported improvement with smoking marijuana was described in 2002 in a patient with central pain and dystonia and in a patient with Wilson disease [8, 9]. Cannabidiol showed improvement of 20–50 % by videotape review in 5 patients [9], but higher doses exacerbated tremor and hypokinesia in 2 patients with PD and levodopa-induced dystonia. Nabilone, a synthetic oral form of Δ^9 -THC, which is available in the USA for other indications, was not found to be effective in 1 administration of escalating doses of 0.03 mg/kg using a dystonia rating scale; however, 3/15 patients felt better for several days after its use [10]. Another currently available oral form of Δ^9 -THC, dronabinol, did not improve symptoms of cervical dystonia, as demonstrated by the Toronto Western Hospital Spasmodic Torticollis Rating Scale in a 3-week treatment trial [5]. Finally, response to dronabinol 2.5 mg twice daily in a case report of dystonia (and tics) in a patient with multiple sclerosis who had previously reported symptom improvement after smoking marijuana [11].

Side effects described in these studies included hypotension and sedation at higher doses of nabilone [10], insomnia and tachycardia from dronabinol [5], and hypokinesia and tremor of PD [10].

Dyskinesias from Levodopa (in Advanced PD)

The plethora of endocannabinoid receptors in the basal ganglia, especially the globus pallidus interna, pars reticulata, and cerebellum indicate they must be playing a role in regulating

tone and motor function through the effect of the endogenous cannabinoid ligand, arachidonylethanolamide (anadamide), on modulation of GABA transmission [12]. Many studies have been done with primate or rat models to determine if cannabinoid agonists or antagonists could act to suppress dyskinesias without exacerbating hypokinesia; however, translation to patients has proved difficult.

Since the initial observation in 1991 of no improvement of resting tremor in 5 patients who smoked one marijuana cigarette [13], surveys have been done asking patients with PD to say if they had tried marijuana on their own (presumably the smoked botanical form) and if so with what effect. Venderova sent surveys to 630 patients attending a movement disorders clinic in Prague, and of the 339 respondents, 25 % had used marijuana. Of these 85 patients, 39 benefitted in rest tremor (31 %), bradykinesia (45 %), and dyskinesias (14 %), and continued its daily use [14]. A recent survey of Colorado residents with Parkinson using all types of complementary therapies found 9 using medical marijuana (4 %), reporting improvement of mood and sleep, but only 2 with improvement of motor symptoms, not specifically dyskinesias [15].

A small but class III randomized double-blind study using nabilone (synthetic Δ^9 -THC) showed a significant reduction in Rush score on levodopa-induced dyskinesias in 7 patients, observed and measured with the Rush dyskinesia scale [16], and 2 reported improvement in dystonia occurring in the off period for dopa. In a study of 17 patients using the oral preparation Cannador (2.5 mg Δ^9 -THC/1.25 mg CBD) no improvement was noted in dyskinesias as measured in Q32–34 of the Unified Parkinson's disease rating scale (the primary outcome), or other scales including Parkinson Disease Questionnaire-39 scale, nor was there a dose response [17]. The study by Carrol et al. [17] was the only one considered class I for the purposes of evidence-based recommendations. Various doses of cannabidiol were given to 21 patients over 6 weeks; no change was found in the total motor score, despite improvement in the quality of life section of the Unified Parkinson's disease rating scale if the target dose of 300 mg daily was reached, which was possible in only 35 % of the patients [18]. Finally, an open-“label” study of smoked marijuana in 22 Israeli patients showed improvement in the number of dyskinesias observed after dopa challenge, 30 min after smoking the cigarette [19]. In an interesting twist, a single dose of the CB₁R antagonist rimonabant (SR141716) was found to have no effect on motor symptoms, or induced dyskinesias in 8 patients [20].

Side effects mentioned in the studies included hypotension, vertigo, hyperacusis, and disorientation and visual hallucinations [15], somnolence, dizziness and bad taste, with hypoglycemia in 1 patient [19], and, rarely, bradykinesia, but in the few studies where it was measured [17], there was no effect on cognitive function as measured by Mini Mental State Examination; in fact, an improvement in Mini Mental State

Examination was noted, which was attributed to a practice effect but may have been precognitive (the 4-week trial was too short to call cannabis neuroprotective).

In summary in PD, the symptom that responded best to cannabis, levodopa-induced dyskinesias, is a fairly rare complication of dopamine replacement in advanced cases. The role of cannabis in other symptoms of PD is unclear, and these symptoms vary according to the stage of neurodegeneration and also to the state of treatment with dopamine transmitter replacement. As there is the potential of cannabis worsening some symptoms, especially hypokinesia, very careful research must be done with PD.

Dyskinesias in HD

Abnormalities of motor function, along with psychiatric and cognitive dysfunction, are a main feature of HD, a dominantly inherited neurodegenerative disease. Cannabis products have been most often used to ameliorate agitation and other psychiatric symptoms, but the presence of endocannabinoid receptors in the striatum, where they modulate GABA transmission and affect glutamate release, suggests a role for management of the excessive involuntary movements (choreoathetosis or dystonia) of HD. As in other degenerative processes, these receptors can decrease as the disease progresses, leaving less response to cannabinoid agonists as the brain's substrate changes. Obviously, current or prior use of dopamine-blocking medication (neuroleptics), which can superimpose tardive dyskinesias on the direct movements of HD, will also change the therapeutic effects of cannabis.

Consroe et al. [21] first reported the clinical use of CBD in HD in 1991. This class III study of 15 patients receiving cannabis extract in capsule form (10 mg/kg), crossing to placebo over a 15-week period, off neuroleptics for at least 2 weeks, found no difference in the chorea severity score of Marsden and Quinn, or on videotape and live assessment of chorea severity, nor on secondary end points of Shoulson and Fahn disability scores, finger tapping, or manipulation. Side effects, as checked off a symptom inventory, did not vary between placebo and treated patients. After a case report in a patient who had improved mood and movements after smoking marijuana and then taking prescribed nabilone, 1 mg daily [22], the authors gave 1 or 2 mg of nabilone to 37 patients in a class II study [23]. Despite improvement in the secondary measures of neuropsychiatric index and chorea score, the primary outcome, total motor score of the Unified Huntington Disease Rating Scale, showed only a modest response, with no dose response (i.e., 2 mg was not better than 1 mg).

Drowsiness and forgetfulness were the main reported adverse events in both groups, with no increase in psychosis or euphoria in the treated group. In 1 case nabilone actually caused increased chorea [24].

Tourette Syndrome Tics

As in any condition influenced by anxiety, a nonspecific beneficial effect of cannabis might be expected, but given the presence of endocannabinoid receptors in the striatum, it is possible that a direct effect of cannabis is reducing the number of tics.

Success in treating symptoms of Tourette syndrome, including involuntary movements (tics) and compulsive behaviors, was first mentioned in an observation of 3 patients who, in 1988, noted improvement in tics and urges while smoking marijuana cigarettes [25], followed by another case of a patient remaining symptom free for a year while smoking marijuana daily [26]. In 1998 a survey of a larger population confirmed a reduction in tic or complete remission in 82 % of patients [27]. The same authors used Δ^9 -THC capsules of varying strengths in a single dose in 12 patients (class II study) and reported improvement in scores of the Tourette Syndrome Symptom List and obsessive-compulsive behavior scores, with a decreased number of complex motor tics observed by the examiner [28]. The following year, in a study of 24 patients using the maximum-strength Δ^9 -THC capsule from the pilot study (10 mg) for 6 weeks, a significant response in self-rated Tourette score and observer-rated scores, including the Tourette Syndrome Clinical Global Impression Scale, the Shapiro Tourette Syndrome Severity Scale, and the Yal Global Tic Severity Scale, as well as the review of video, was noted [29]. These were then summarized in a Cochrane review [30]. Little additional work was summarized in a more recent review [31]. Of note, improvements occurred without exacerbating performance on neuropsychologic testing [32].

Side effects were minimized by a simple technique of providing dronabinol after breakfast in order to slow its absorption and provide a steady level acting in the brain [29].

Conclusions

Although clinical studies in this area are difficult to do, even in countries where the use of cannabis has been allowed for years, there is a clear role for cannabis products in symptom management for these difficult conditions. The movement disorders are well-known to be worsened in patients who are anxious, but the careful observations reviewed above lead to the conclusion that there is a direct effect of cannabis in various formulations in some conditions, especially hyperkinetic symptoms. Caution in using a potential central nervous system depressant is always required in patients whose neurologic function is already compromised by disease, but

larger studies will prove there is a promising role for this class of drug in the therapy of dyskinesias, tics, and possibly dystonia.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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Published in final edited form as:

J Drug Policy Anal. ; 4(1): . doi:10.2202/1941-2851.1017.

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.

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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%	<i>0.010</i>
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%	<i>0.001</i>
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%	<i>0.000</i>
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%	<i>0.001</i>
Some college*	27.1%	31.0%	25.6%	<i>0.031</i>
College graduate*	21.6%	24.7%	20.4%	0.064
Employed	68.7%	60.4%	71.8%	<i>0.000</i>
Disabled	15.5%	19.5%	14%	<i>0.006</i>
Previous military service	10.5%	2.1%	13.6%	<i>0.000</i>
Currently insured	73.0%	78.2%	71.1%	<i>0.004</i>
Worker's comp	3.5%	2.9%	3.7%	0.394
MediCare	9.2%	11.9%	8.2%	<i>0.020</i>
MediCal	15.0%	21.7%	12.6%	<i>0.000</i>
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

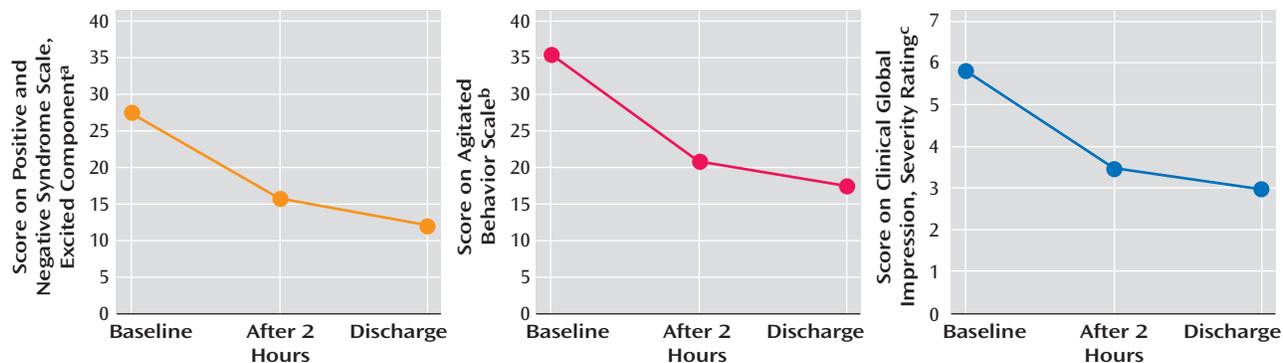
Note: Does not include all ICD9s, and excludes those that were written in.

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%	0.000
1–2 prescriptions	36.7%	36.1%	37.0%	0.727
3–5 prescriptions	4.4%	9.1%	2.7%	0.000
6+ prescriptions	6.5%	11.9%	4.5%	0.000
Previous prescription medication	79.5%	86.5%	76.8%	0.000
Past or current RX for opioids for pain	48.0%	52.3%	46.4%	0.040
Physical therapy	48.6%	54.4%	46.5%	0.004
Chiropractic	37.2%	42.3%	35.2%	0.009
Surgery	21.9%	22.3%	21.8%	0.804
Psychological counseling	20.7%	33.4%	16.0%	0.000
Acupuncture	19.6%	26.8%	16.9%	0.000
Therapeutic injection	15.0%	21.5%	12.6%	0.000
Other types of treatment	8.6%	11.1%	7.7%	0.032
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%	0.006
Psychological counseling	5.6%	7.1%	5.0%	0.098
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

FIGURE 1. Scores of Agitated Patients After the First Intramuscular Injection With Olanzapine



^a $t=10.59$, $p<0.0001$

^b $t=12.00$, $p<0.0001$

^c $t=11.43$, $p<0.0001$

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CRISTIAN DAMSA, M.D.
Geneva, Switzerland

ERIC ADAM, M.Sc.

Liège, Belgium

CORALIE LAZIGNAC, M.D.

ADRIANA MIHAI, M.D.

Geneva, Switzerland

FRANCOIS DE GREGORIO, M.D.

Liège, Belgium

Geneva, Switzerland

JOSEPH LEJEUNE, M.D.

Liège, Belgium

SUSANNE MARIS, M.Sc.

EMMANUEL CLIVAZ, M.D.

Geneva, Switzerland

MICHAEL H. ALLEN, M.D.

Denver, Colo.

The authors report no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07060946) was accepted for publication in October 2007.

Improvement in Refractory Obsessive Compulsive Disorder With Dronabinol

TO THE EDITOR: It has been reported that 40%–60% of patients with obsessive-compulsive disorder (OCD) do not respond to first-line treatment. Treatment options for these patients include switching to another agent or augmentation (1). We report on two patients with treatment-resistant OCD and comorbid axis I disorders who responded to an augmentation with the cannabinoid dronabinol.

“Mrs. L” was a 38-year-old woman who was admitted with recurrent major depression and OCD (Yale-Brown Obsessive Compulsive Scale score: 20) after outpatient treatment with paroxetine (60 mg) for 8 months and cognitive behavioral therapy (CBT) were not efficacious. Switching to clomipramine (300 mg) resulted in partial response after 12 weeks of treatment. Based on the patient’s report that smoking marijuana usually relieved her symptoms, an augmentation with dronabinol (2.5%; 10 mg t.i.d.) was started. The prior medication was continued. While undergoing treatment with dronabinol (2.5%), the patient’s OCD symptoms decreased significantly within 10 days (Yale-Brown Obsessive Compulsive Scale score: 10).

“Mr. K” was a 36-year-old man with schizophrenia and OCD who was admitted for deterioration of psychotic and obsessive symptoms (Yale-Brown Obsessive Compulsive Scale score: 23). During his course of illness, Mr. K had been treated with antipsychotics (including haloperidol, olanzapine, risperidone, quetiapine, and aripiprazole), both in monotherapy and in combination with selective serotonin reuptake inhibitors. His OCD symptoms in particular remained predominately treatment resistant. Treatment with clozapine (400 mg), which he had already received for more than 1 year (in combination with paroxetine [60 mg] for 13 weeks) resulted only in partial response of his psychotic and OCD symptoms. Switching paroxetine to clomipramine (for another 10 weeks), followed by an additional course of 18 electroconvulsive therapy treatments (right unilateral high dose), did not improve the patient’s psychotic or OCD symptoms significantly. After the addition of dronabinol to ongoing treatment with clomipramine (150 mg) and clozapine (400 mg), a significant reduction of OCD symptoms was observed within 2 weeks (Yale-Brown Obsessive Compulsive Scale score: 15). In order to prevent psychotic deterioration, dronabinol (2.5%) was carefully increased to 10 mg b.i.d.

Apart from anticholinergic symptoms that preceded the addition of dronabinol (patient 1: dry mouth, constipation; patient 2: constipation, hypotension), both patients reported no side effects. In particular, there was no deterioration of psychotic or mood disorder symptoms.

Based on data from case reports and small clinical trials suggesting that cannabinoids can reduce symptoms of tic disorder (2) and on findings from genetic studies linking tic disorder with OCD (3), we hypothesized that cannabinoids

might also reduce OCD symptoms. Moreover, there is evidence suggesting that besides serotonergic and dopaminergic systems, glutamatergic hyperactivity is involved in the pathophysiology of OCD (4, 5). This view is supported by data suggesting the efficacy of glutamate modulating drugs, such as topiramate, memantine, riluzole, or N-acetylcysteine, in the treatment of OCD (6). It has been reported that cannabinoids inhibit glutamate release in the CNS (7, 8). Additionally, cannabinoid type 1 (CB₁) receptors are distributed abundantly in the striatum (8), a brain region frequently associated with OCD. Hence, it can be speculated that the anti-obsessive effect observed in our patients may have been a consequence of the glutamate modulation of the cannabinoid dronabinol. Since it is well known that cannabinoids may trigger psychotic symptoms in patients with schizophrenia (8), caution is warranted when prescribing for patients with a history of the disorder.

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FRANK SCHINDLER, M.D.
ION ANGHELESCU, M.D., PH.D.
FRANCESCA REGEN, M.D.
MARIA JOCKERS-SCHERUBL, M.D., PH.D.
Berlin, Germany

The authors report no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07061016) was accepted for publication in September 2007.

Maintenance Treatment With Transcranial Magnetic Stimulation in a Patient With Late-Onset Schizophrenia

TO THE EDITOR: A recent meta-analysis (1) concluded that repetitive transcranial magnetic stimulation (rTMS) efficiently reduces resistant auditory hallucinations in patients with schizophrenia (effect size=0.76). Nevertheless, treatment is

presently only provided over short periods of time, and little is known about longer-term impact. Maintenance treatment protocols have been developed, and we previously described a case report involving a maintenance protocol with a weekly, once-a-day stimulation (2); however, we failed to demonstrate long-term benefits. To our knowledge, the case presented below is the first report of a twice-daily transcranial magnetic stimulation as efficacious for auditory hallucinations, both in acute and maintenance treatment.

“Ms. A,” a 55-year-old right-handed, postmenopausal woman who had DSM-IV late-onset schizophrenia with an illness duration of 2 years, was referred for transcranial magnetic stimulation treatment. She was noted to have benzodiazepine addiction involving the use of lorazepam (9 mg/day). She had been suffering from resistant auditory hallucinations for 2 years (very frequent and loud, with >5 critical and command voices). She was unresponsive to four antipsychotic medication trials lasting >4 months each, including haloperidol (5 mg/day), amisulpride (1200 mg/day), olanzapine (15 mg/day), and risperidone (8 mg/day). A detailed assessment did not reveal any other pathology or transcranial magnetic stimulation contraindications. Auditory hallucinations were assessed using the Auditory Hallucination Rating Scale (3), and positive symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS). Lorazepam withdrawal was completed without exacerbation of the psychotic symptoms (Auditory Hallucination Rating Scale score: 34). Four months after her initial presentation, the patient gave informed consent and was included in a transcranial magnetic stimulation protocol. Twice-a-day, 1000 low-frequency repetitive stimulations (1 Hz) were administered to the temporoparietal cortex at 100% of motor threshold over a 5-day period. The patient's current dose of risperidone was maintained during treatment with transcranial magnetic stimulation. After the first course, auditory hallucinations were moderately improved, with a 35% reduction in her Auditory Hallucination Rating Scale score, which did not change over the next several months, as observed in a follow-up assessment. However, the patient's general SAPS score improved, with a 30% reduction in severity.

Six months after the first course of transcranial magnetic stimulation therapy, the patient presented with a relapse of hallucinations. A new transcranial magnetic stimulation course, with the same parameters, was conducted. This second course was followed by a once-per-month, twice-daily maintenance protocol (one session in the morning, the other in the afternoon on the same day). The patient's auditory hallucinations were greatly improved, by 80%, and her SAPS score decreased from 38 to 16. This maintenance course was associated with a remission of auditory hallucination symptoms, with a stabilization of SAPS scores at 10 over the next 6 months. Presently, more than 1 year later, Ms. A is not receiving any antipsychotic medication, and her Auditory Hallucination Rating Scale and SAPS scores remain at 0.

Our case raises the question as to whether twice-daily transcranial magnetic stimulation may be useful in some patients as a possible maintenance intervention. Certainly, further research will help us to understand whether the benefits observed in this single case might also be evident in larger studies.

RESEARCH ARTICLE

The Relationship between Bipolar Disorder and Cannabis Use in Daily Life: An Experience Sampling Study

Elizabeth Tyler^{1*}, Steven Jones¹, Nancy Black², Lesley-Anne Carter³, Christine Barrowclough²

1 The Spectrum Centre for Mental Health Research, Division of Health Research Lancaster University, Lancaster, Lancashire, United Kingdom, **2** School of Psychological Sciences, University of Manchester, Manchester, United Kingdom, **3** Health Methodology Research Group, School of Community Based Medicine, University of Manchester, Manchester, United Kingdom

* e.tyler@lancaster.ac.uk



OPEN ACCESS

Citation: Tyler E, Jones S, Black N, Carter L-A, Barrowclough C (2015) The Relationship between Bipolar Disorder and Cannabis Use in Daily Life: An Experience Sampling Study. PLoS ONE 10(3): e0118916. doi:10.1371/journal.pone.0118916

Academic Editor: Marianna Mazza, Catholic University of Sacred Heart of Rome, ITALY

Received: May 28, 2014

Accepted: January 22, 2015

Published: March 4, 2015

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Data Availability Statement: The readers can contact the Corresponding Author for data that cannot be made publicly available due to an ethical restriction: Dr Elizabeth Tyler e.tyler@lancaster.ac.uk. Spectrum Centre for Mental Health Research Division of Health Research Furness Building Lancaster University LA1 4YG. The other data files are provided as Supporting Information.

Funding: The study was funded by the PARADES programme grant (RP-PG-0407-10389) led by Professor Steven Jones which was funded by National Institute for Health Research (NIHR), UK and the University of Manchester, UK Doctorate of

Abstract

Objectives

Although cannabis use is common in bipolar disorder and may contribute to worse clinical outcomes, little is understood about the relationship between this drug and bipolar disorder over the course of daily life. The aim of study was to examine the effect of cannabis on affect and bipolar symptoms in a group of individuals with bipolar disorder.

Methods

Twenty-four participants with bipolar disorder type I or type II completed diaries for 6 days using Experience Sampling Methodology to investigate the temporal associations between cannabis, affect and bipolar disorder symptoms.

Results

The results indicated that higher levels of positive affect increase the odds of using cannabis (OR:1.25 ,CI:1.06–1.47, P=0.008). However, neither negative affect, manic nor depressive symptoms predicted the use of cannabis. Cannabis use was associated with subsequent increases in positive affect ($\beta=0.35$, CI:0.20-0.51, P=0.000), manic symptoms ($\beta=0.20$, CI:0.05-0.34, P=0.009) and depressive symptoms ($\beta=0.17$,CI:0.04-0.29, P=0.008).

Conclusion

The findings indicate that cannabis use is associated with a number of subsequent psychological effects. However there was no evidence that individuals with BD were using cannabis to self-medicate minor fluctuations in negative affect or bipolar disorder symptoms over the course of daily life. The findings in relation to existing literature and clinical implications are discussed.

Clinical Psychology training course. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

Cannabis is the street drug most frequently used by individuals with bipolar disorder (BD) [1, 2, 3]. Estimates of current use range from 8% to 22% and lifetime use from 30% to 64% [4]. Cannabis use in BD is associated with poorer outcomes, including increased symptom severity [5] and poorer treatment compliance [5, 6]. A recent study found that individuals who were diagnosed with BD and a co-occurring cannabis disorder had a younger age of BD onset and an increased number of manic, hypomanic and depressive episodes per year [7].

Specific reasons for the high levels of cannabis use in BD remain equivocal and are not yet fully understood. Whilst there have been a number of reviews reporting on the co-occurrence of substance use and BD [8] few studies have focused specifically on the relationship between cannabis use and BD [7].

Prospective cohort studies [9, 10, 11] have found evidence to suggest that cannabis use begins prior to bipolar onset, which might suggest a causal role in the development of BD. However there is also evidence to suggest that for some, cannabis use commences following the onset of manic symptoms [12]. Self-report literature including case histories [13, 14] and qualitative interviews [15] suggests that individuals with BD use cannabis as a form of self-medication to alleviate manic symptoms [13, 15] and to relieve depression [14]. These findings [13, 14, 15] are consistent with the proposal of Ashton et al [16] that the key constituents of cannabis, Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), can have both sedative and antidepressant effects. Therefore whilst manic, individuals may use cannabis for the sedative effects and when depressed for the anti-depressive effects.

As with BD, rates of cannabis use in individuals with psychosis are high [17, 18] and there is no single model available which fully explains this co morbidity [19]. A recent study [20] used the experience sampling method (ESM) to provide further insight into the complicated dynamics of cannabis use and its effect on individuals with psychosis, in the context of daily life. Henquet et al [20] found that cannabis use predicted an increase in positive affect in both individuals with psychosis and a non-clinical control group. Cannabis use also predicted a decrease in negative affect and an increase in the number of hallucinatory experiences in the psychosis group alone. They found no evidence to support the self-medication hypothesis as neither psychotic experiences or mood was found to predict cannabis use. The current study was similarly designed using ESM to allow a close investigation into BD and cannabis use over the course of daily life and to aid further understanding of this seemingly complex relationship.

ESM is a structured diary method where individuals are asked to report their thoughts, feelings and symptoms over the course of daily life. ESM was pioneered in mental health research by researchers at the University of Maastricht [21, 22]. The methodology offers a number of advantages in comparison to traditional assessments of mental health experiences [23, 24], which rely on using retrospective data, and may be open to recall bias. With ESM, the short space between an event occurring and reporting of the details reduces the possibility of memory bias [25]. ESM examines phenomena in the real world as they occur and therefore has a high level of ecological validity. It provides a rich and descriptive data set, detailing a participant's daily experience and has the capacity to assess the temporal relationship between numerous variables [24].

ESM has previously been used to investigate the perception of daily 'hassles' and 'uplifts' in individuals with BD [26]. The study found that individuals who had more previous depressive episodes and current depressive symptoms experienced negative events as more stressful [30]. Furthermore, Knowles et al [27] used a diary method, where individuals with remitted BD or remitted unipolar depression plus a non-clinical sample reported on self-esteem and positive and negative affect twice a day, over the course of a week. The study reported instability of self-esteem and affect in the remitted BD individuals compared to both other groups.

To the authors knowledge there are no published studies that have used ESM to examine the relationship between BD and cannabis use. Therefore the current study aimed to provide an investigation into the associations between cannabis use, positive affect, negative affect and BD symptoms (mania and depression) in individuals with BD in daily life over a six day period, and to test two key predictions suggested in the literature outlined above:

- 1]. frequency of cannabis use will increase as a function of affect and BD symptom change (i.e. self medication effects)
- 2]. cannabis use will be associated with subsequent changes in affect and BD symptoms

Materials and Methods

Ethics statement

Full ethical approval for the study was obtained from Liverpool National Research Ethics Service (NRES) Committee and the University of Manchester research ethics committee. Written, informed consent was obtained from all participants in the study.

Participants

Twenty-nine participants were recruited for the study from a number of sources. These included four mental health trusts in the North-West of England, self-help organisations (Bipolar UK and Mood Swings Network) and self-referral from the online University of Manchester research volunteering website (<http://www.studentnet.manchester.ac.uk/volunteer/>).

All individuals met criteria for BD-I or BD-II, as determined by the Structured Clinical Interview for Axis I Disorders (SCID) based on the DSM-IV diagnostic criteria [28]. Current symptomatology was assessed using the Hamilton Rating Scale for Depression [29] and the Bech Rafaelson Mania Rating Scale [30]. Substance use disorders were assessed using the substance use module of the SCID [28]. To be included, participants were required to report using cannabis on at least two occasions per week (in at least half the weeks in the 3 months prior to assessment). Exclusion criteria for the study included meeting criteria for a current episode of mania or depression (if currently met criteria they were kept on a waiting list until out of episode, except for those who remained unwell throughout the recruitment period), aged below 18, evidence of an organic brain disease or moderate/severe learning disability.

Experience sampling method and procedure

At the beginning of this study, participants were given a paper diary and a digital wristwatch. In accordance with previous research [31, 32], the ESM period lasted for six consecutive days and the watch emitted a signal on ten occasions throughout the day at unpredictable times, between the hours of 8am and 10pm.

Each time participants heard the beep they were required to fill out a page of the diary. The diary consisted of questions on thoughts, affect, BD symptomatology, contextual information regarding their current situation and substance use. Participants were required to fill out the diary within 15 minutes of hearing the beep and to record the time of completion. Any entries completed outside this time frame were excluded from analyses. Previous research has demonstrated that entries completed after the 15 minutes are less reliable and valid [22]. A minimum of 20 valid diary reports were required by each participant, to ensure the data was representative [24].

During the initial visit informed consent was gained from the participant and the SCID [28], Hamilton Rating Scale for Depression [29] and the Beck Rafaelson Mania Rating Scale

[30] were completed. Where all inclusion criteria were met, a second visit was arranged, one day prior to the ESM period. During the second visit, the participant was introduced to the watch and paper diary and briefed about the study. The general procedure described above was explained in detail. On the seventh day a final meeting was arranged to collect the watches and diaries and debrief the participant.

Measures

The ESM diary—affect items

Current affect was assessed using ten items, rated on a 7-point Likert scale (where 1 = 'not at all' and 7 = 'very much so'). In previous ESM studies [20,31,33], with individuals with psychosis and healthy controls, a positive and negative affect scale was identified using a factor analysis on the raw-within participant scores for the affect items ($N = 10$). A principal components analysis for this study was conducted and like the similar studies [20,31,33] revealed two separate scales. The items 'cheerful', 'excited', 'relaxed', 'satisfied', 'happy' formed the positive affect scale ($\alpha = 0.85$) and the items 'lonely', 'anxious', 'irritated', 'sad', 'guilty', formed the negative affect scale ($\alpha = 0.82$). This analysis yielded similar results to other ESM studies. Henquet et al [20] reported a positive affect scale ($\alpha = 0.89$) and a negative affect scale ($\alpha = 0.80$). The mean scores for each scale were used in the analyses.

The ESM diary—BD Symptoms

Current BD symptomatology (mania and depression) was assessed using 7 items rated on a 7-point Likert scale. The items were formulated by the authors (SJ, CB, ET), all of whom had significant experience of working with people with BD. They were chosen in accordance with guidelines for selection of ESM items [24] and to assess momentary experiences of BD symptoms that might reasonably occur and fluctuate during the flow of daily life. A service-user group of 4 people with a BD diagnosis took part in a consultation exercise and checked the appropriateness of the potential questions. Members reported that the language reflected how they would describe their own behaviour and experiences. A principal components analysis revealed two distinct subscales with high internal consistency. The mania scale ($\alpha = 0.76$) consisting of the items: I am 'full of energy', 'high', 'full of good ideas' and the depression scale ($\alpha = 0.83$), consisting of items: I feel 'slowed down', 'low', 'bad about myself', 'fearful'. The mean scores for each scale were used in the analyses.

The ESM diary—substance use

Cannabis use, referred to as a 'cannabis moment' was reported in the diary after each beep (the period between the current beep and previous beep). Information was derived from the question (since the last beep I've used cannabis 'Yes' or 'No?') Cannabis use **previous** was defined as cannabis use during the period between previous beep and the beep before that. The type of cannabis used was also recorded (skunk, resin or grass).

Alcohol and drug use other than cannabis were reported in the diary after each beep, termed 'alcohol moment' and 'other drug moment' respectively.

Statistical analysis strategy

STATA 11 [34] was used for the analyses. ESM data has a hierarchical structure with the repeated participant observations (level one), nested within days (level two), nested within participants (level three). Responses for one individual or for one day are more likely to be similar than those for a different individual or for a different day. Multilevel random regression

analysis was used as it takes the whole data set into account and can estimate the amount of variation that is associated with the three different levels. The multilevel regression XTMELOGIT routine was used for the dichotomous variables and the XT MIXED routine for the continuous variables. Therefore the odds ratios (dichotomous variables) and the betas (continuous variables) are the associations between the independent and dependent variables in the multilevel model.

Preliminary analyses

Multi-level regression analyses were conducted to identify whether age, gender, alcohol use at the same beep, other drug use at the same beep, type of cannabis used and total cannabis use for the ESM period were associated with changes in affect, BD symptoms and cannabis use. The results were used to identify which variables would be adjusted for in the main analyses.

Self medication effects

To investigate whether affect or BD symptoms predicted cannabis use; multilevel analyses were conducted using the XTMELOGIT routine. Positive affect **previous**, negative affect **previous**, mania **previous** and depression **previous** were entered as the independent variables and cannabis use as the dependent variable. Overall cannabis use during the ESM week was adjusted for in these analyses.

Cannabis effects on affect and BD symptoms

The main effects of cannabis use on affect / symptoms were investigated with cannabis use as the independent variable and positive affect, negative affect, mania and depression as the dependent variables. Alcohol use at the same beep and overall cannabis use during the ESM week were adjusted for in these analyses.

Temporal analyses of cannabis use

Post hoc analyses were conducted to further investigate the duration of cannabis effects on affect and symptoms. To investigate these, cannabis use at the current beep and cannabis use **previous** were entered simultaneously into the model, predicting positive affect, negative affect, mania and depression.

Results

Participants

Twenty-nine participants initially participated in the study. However three participants were subsequently excluded as they had fewer than 20 valid reports and a further two dropped out due to personal circumstances. The final study sample consisted of 24 participants. See [table 1](#) for socio-demographics of the participant sample.

Participant exclusion /drop outs

Five participants were excluded / dropped out of the study. There were no significant differences between individuals who completed the study and those who did not in relation to gender, ethnicity, bipolar diagnosis, marital status, occupational status or living arrangements. However significant differences were revealed between the two groups in terms of age. Individuals who were excluded/ dropped out had a higher mean age and scores on the HAM and the MAS were elevated for the group that was excluded/ dropped out (see [table 2](#) for actual values).

Table 1. Socio-demographics of the participant sample.

Gender (F:M)	8:16
Age Mean (SD)	37.1 (12.6)
Diagnosis (BDI: BD II)	22.2
Current HAM mean (SD)	7.7 (7.2)
Current MRS mean (SD)	2.9 (3.3)
Ethnicity	
White British	21 (88%)
Other White Background	1 (4%)
Black Caribbean	1 (4%)
White and Asian	1 (4%)
Living status	
Living alone	12 (50%)
Living with friends	5 (21%)
Living with partner and/or children	6 (25%)
Living with close relative	1 (4%)
Occupation	
Sick/ Disability	14 (58%)
Student	4 (17%)
Employed/ self employed	3 (13%)
Employed voluntary	2 (8%)
Unemployed	1 (4%)
Medication	
Prescribed mood stabilizer	20 (83%)
No mood stabilizer	4 (17%)
Co-morbidity (current)	
Anxiety disorders *	6 (25%)
Personality disorders **	5 (21%)

* Anxiety disorders included panic disorder (with and without agoraphobia), generalised anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, social phobia, specific phobia.

** Personality disorders included Borderline personality disorder and anti-social personality disorder

doi:10.1371/journal.pone.0118916.t001

Substance use

Three participants met current criteria for cannabis abuse disorder and 12 met criteria for current cannabis dependence disorder. Over the course of the six-day ESM period, the mean number of cannabis moments for the sample was 15.0 (SD: 8.6, range: 2–30). During this period all participants reported only using one type of cannabis, with the majority using ‘skunk’ (54%). The mean number of alcohol moments for the sample was 3.1 (SD: 5.5, range 0–21) and for ‘other’ drug use 0.8 (S.D: 2.5, 0–12). See [table 3](#) for other drug and alcohol use.

Preliminary analyses

Age, gender, other drug use (at the same beep) and type of cannabis used were not associated with any of the outcome variables, therefore were not adjusted for in the main analyses. Total cannabis use for the ESM period (number of cannabis moments) was positively associated with cannabis use at the current beep ($\beta = 0.12$, 95% CI: 0.10–0.15, $P = 0.000$), therefore this was adjusted for in all the main analyses. Alcohol use (at the same beep) was positively associated with subsequent increases in positive affect ($\beta = 0.48$, 95% CI: 0.21–0.74, $P = 0.000$) and manic

Table 2. Socio-demographics of the dropped out / excluded sample.

Gender (F:M)	1:4
Age Mean (SD)	44.6 (12.1)
Diagnosis (BD I: BD II)	5:0
Current HAM mean (SD)	8.25 (8.5)
Current MRS mean (SD)	4.25 (3.1)
Ethnicity	
White British	5 (100%)
Other White Background	0
Black Caribbean	0
White and Asian	0
Living Status	
Living alone	3 (60%)
Living with friends	0
Living with partner and / or children	2 (40%)
Living with close relative	0
Occupation	
Sick / Disability	5 (100%)
Student	0
Employed/ self-employed	0
Employed voluntary	0
Unemployed	0

doi:10.1371/journal.pone.0118916.t002

Table 3. Substance abuse in the participant sample.

Cannabis	
Current abuse	3 (13.0%)
Current dependence	12 (50%)
Type of cannabis used	
Skunk	13 (54%)
Resin	8 (33%)
Grass	3 (13%)
Cannabis moments over ESM period	
Mean (S.D)	15.0 (8.6)
Range	2–30
Alcohol	
Current abuse	2 (8%)
Current dependence	1 (4%)
Alcohol moments over ESM period	
Mean (S.D)	3.1 (5.5)
Range	0–21
Other drug use	
Current abuse	2 (8%)
Current dependence	1 (4%)
Other drug moments over ESM period	
Mean (S.D)	0.8 (2.5)
Range	0–12

doi:10.1371/journal.pone.0118916.t003

Table 4. Effect of mood/ BD symptomatology on cannabis use (Self-medication effects).

Positive affect	OR: 1.25, 95% CI: 1.06–1.47, P = 0.008
Negative affect	OR: 0.88, 95% CI: 0.74–1.05, P = 0.147
Mania scale	OR: 1.08, 95% CI: 0.93–1.26, P = 0.291
Depression scale	OR: 0.92, 95% CI: 0.78–1.08, P = 0.303

doi:10.1371/journal.pone.0118916.t004

symptoms ($\beta = 0.40$, 95% CI: 0.15–0.65, $P = 0.002$), therefore it was adjusted for in the analyses which investigated the effects of cannabis.

Self—medication effects

There was a significant positive relationship between positive affect **previous** and cannabis use at the current beep (OR: 1.25, 95% CI: 1.06–1.47, $P = 0.008$). The odds of cannabis use at the current beep were increased for those with higher scores of positive affect at the previous beep. Negative affect **previous** did not significantly predict cannabis use at the following beep (OR: 0.88, 95% CI: 0.74–1.05, $P = 0.147$). Similarly no association was found between manic symptoms **previous** (OR: 1.08, 95% CI: 0.93–1.26, $P = 0.291$) or depressive symptoms **previous** (OR: 0.92, 95% CI: 0.78–1.08, $P = 0.303$) and cannabis use. See [table 4](#).

Cannabis effects on affect and BD symptoms

Cannabis use was associated with subsequent increases in positive affect ($\beta = 0.35$, 95% CI: 0.20–0.51, $P = 0.000$). Cannabis use was also associated with subsequent increases in manic symptoms ($\beta = 0.20$, 95% CI: 0.05–0.34, $P = 0.009$) and depressive symptoms ($\beta = 0.17$, 95% CI: 0.04–0.29, $P = 0.008$). Overall, cannabis use had no effect on negative affect ($\beta = -0.01$, 95% CI: -0.13–0.10, $P = 0.806$). (See [table 5](#)).

Temporal dynamics of cannabis effects

Follow up post-hoc analyses were conducted to investigate the duration of cannabis effects on affect and BD symptoms. This was achieved by entering cannabis use and cannabis use **previous** simultaneously into the model. The results suggested that increases in positive affect were observed in the short term ($\beta = 0.29$, 95% CI: 0.10–0.48, $P = 0.003$ for cannabis use) but not the longer term (over one beep but not two) ($\beta = 0.01$, 95% CI: -0.18–0.20, $P = 0.943$ for cannabis use **previous**). Similarly increases in depressive symptoms were observed in the short term ($\beta = 0.18$, 95% CI: 0.03–0.33, $P = 0.019$ for cannabis use) but not the long term ($\beta = 0.11$, 95% CI: -0.04–0.27, $P = 0.138$ for cannabis use **previous**). For mania, when both cannabis use and cannabis use **previous** were entered simultaneously in the same model, increases in manic symptoms were not observed in the short term ($\beta = 0.07$, 95% CI: -0.10–0.24, $P = 0.393$) or long term ($\beta = -0.08$, 95% CI: -0.25–0.09, $P = 0.359$). See [table 6](#).

Table 5. Effect of cannabis use on mood/ BD symptoms.

Positive affect	$\beta = 0.35$, 95% CI: 0.20–0.51, $P = 0.000$
Negative affect	$\beta = -0.01$, 95% CI: -0.13–0.10, $P = 0.806$
Mania Scale	$\beta = 0.20$, 95% CI: 0.05–0.34, $P = 0.009$
Depression Scale	$\beta = 0.17$, 95% CI: 0.04–0.29, $P = 0.008$

doi:10.1371/journal.pone.0118916.t005

Table 6. Temporal dynamics of cannabis effects.

Positive affect	
Cannabis use	$\beta = 0.29$, 95% CI: 0.10–0.48, $P = 0.003$
Cannabis use previous	$\beta = 0.01$, 95% CI: -0.18–0.20, $P = 0.943$
Negative affect	
Cannabis use	$\beta = -0.04$, 95% CI: -0.18–0.10, $P = 0.579$
Cannabis use previous	$\beta = -0.01$, 95% CI: -0.15–0.13, $P = 0.925$
Mania Scale	
Cannabis use	$\beta = 0.07$, 95% CI: -0.10–0.24, $P = 0.393$
Cannabis use previous	$\beta = -0.08$, 95% CI: -0.25–0.09, $P = 0.359$
Depression Scale	
Cannabis use	$\beta = 0.18$, 95% CI: 0.03–0.33, $P = 0.019$
Cannabis use previous	$\beta = 0.11$, 95% CI: -0.04–0.27, $P = 0.138$

doi:10.1371/journal.pone.0118916.t006

Discussion

Higher levels of positive affect increase the odds of using cannabis, however neither negative affect, manic symptoms nor depressive symptoms predicted the use of cannabis at the subsequent beep. The data from the current study indicates that individuals with BD are not using cannabis to self-medicate minor fluctuations in negative affect and bipolar symptoms (previous beep to current beep). It remains to be seen how this data relates to the broader self-medication hypothesis in BD. In line with the second prediction, the findings from the study indicate that the use of cannabis in daily life was associated with subsequent increases in positive affect, manic symptoms and depressive symptoms. In addition, the data suggests that increases in positive affect and depressive symptoms were only experienced in the short-term, as cannabis use at the previous beep did not predict a significant increase in affect or symptoms at subsequent time points.

Cannabis effects

The findings that cannabis use was associated with an increase in positive affect, manic and depressive symptoms is consistent with current literature that suggests cannabis can produce a range of psychological effects [35, 36, 37]. It has been suggested that the psychological and physiological effects of cannabis are primarily due to its main chemical compounds, THC and CBD. The effects of cannabis have previously been found to be bidirectional [35, 38], causing effects such as euphoria and dysphoria; this may partially explain why cannabis use was associated with both manic and depressive symptoms in the current study. The bidirectional effects of cannabis have been found to depend on a range of factors such as dose, route of administration and personality differences [35, 38].

The effect of cannabis use on individuals with psychosis has received rather more investigation than the effects of the drug on those with BD. Research suggests that compared to ‘healthy’ control participants, individuals with at high risk for psychosis may be more sensitive to THC [39, 40]. Barkus and Lewis [41] found that individuals scoring higher on Schizotypal traits were more likely to experience both psychosis-like experiences and more pleasurable experiences after smoking cannabis. Individual differences in sensitivity to the effects of THC may explain the range of experiences, as noted by Henquet et al [20]. In a similar way, individuals with BD may also differ in their sensitivity to the effects of THC, which may explain why there was a range of effects in the current study.

Effects of affect / BD symptoms on cannabis use (Self-medication effects)

The results indicated that higher levels of positive affect increase the odds of using cannabis, and it appears that individuals were using cannabis when they were feeling good. Alternatively, higher positive affect prior to cannabis use may have been experienced due to the expected enjoyment of the effects of substance use.

Data from the current study does not support the idea that cannabis is used by individuals with BD for the self-medication of minor fluctuations in negative affect and BD symptoms in the context of daily life. An increase in negative affect and BD symptoms did not predict cannabis use at the following beep. This finding is consistent with Henquet et al [20] who similarly did not find evidence to support the self-medication hypothesis for psychosis over the course of daily life, as changes in hallucinations, delusions and negative affect did not predict cannabis use.

The interpretation of the findings of this study is limited to the associations between the current beep and the previous beep. It is possibly the case that self-medication effects appear further down the chain of events, following a longer period of negative affect / symptom changes. Alternatively, failure to find self-medicating effects from cannabis may have been due to the nature of the participant sample. BD is characterised by shifts in affect regulation and therefore over time individuals may have become accustomed to subtle changes in mood. Therefore, within the context of daily life, cannabis may not be used as a way to cope with these slight fluctuations. Participants in the study were currently well and out of episode and therefore it may be that cannabis is used to self-medicate more pronounced symptoms or the onset of manic / depressive episodes. This would be consistent with the self-report literature where individuals have found cannabis useful in the management of their BD [13, 14, 15].

Limitations

Several limitations need to be taken into account in interpreting the results of the study. First, details of cannabis use were based on self-report. Cannabis use remains illegal in the United Kingdom, and this may have led to underestimations in reported use. Hair sample analysis may have offered a way to confirm usage [42], however this was beyond the resources of the current study. Additionally, whilst type of cannabis was reported and adjusted for in analyses, the individual potency of the drugs consumed was not controlled for. There are in excess of 100 different strengths of cannabis and research has revealed that on average, cannabis resin and herbal (grass) contains around 2–4% THC, however Sinsemilla (Skunk) contains around 12–18% THC [43, 44]. Data for cannabis use at each beep was dichotomized into 'yes' or 'no'; future studies might attempt to collect and report information regarding the amount of cannabis ingested and route of consumption at each beep.

The items used on the scales for mania and depression were formulated specifically for use in the ESM diary in this study. They were chosen in accordance with guidelines for the selection of ESM questions [24] which highlights the need for items to be 'momentary experiences which occur in the flow of daily life'. Whilst we have limited evidence for their validity, items were reviewed by a service user panel with BD who felt they accurately described their experience when manic and depressed. A correlation matrix was computed to investigate the relationship between the positive affect, negative affect, mania and depressive scales. There was a strong correlation between the negative affect and depressive scales ($r = 0.82$). This indicates that there may have been a high degree of overlap between the scales. The correlation between the positive affect scale and mania scale was ($r = 0.58$). However during the main analyses the scales produced different results (e.g. cannabis use was significantly associated with depressive

symptoms but not with negative affect and higher levels of positive affect increase the odds of using cannabis, however higher levels of manic symptoms did not). This provided some predictive validity to support the use of separate scales: and it suggests that they were measuring different emotional states. Items from the positive and negative affect scales were considered to reflect everyday mood fluctuations as expected within the 'normal' range. The items formulated for the mania and depression scales were deemed to reflect symptoms specific to BD that would fluctuate over the course of daily life.

Cannabis is known to have an impact on cognition [45, 46] and as suggested by Henquet et al [20] this may therefore have impacted on the ability to report information accurately in the diaries. However one of the main advantages of using ESM is the short space of time between an event occurring and the recall, which reduces memory bias [25]. Additionally, a recent study [47] found cannabis use was associated with better neuro-cognitive functioning in participants with BD, particularly executive functioning.

Cannabis is rapidly metabolized in the body and the pharmacological effects can often begin within minutes after smoking [48]. Blood plasma levels of THC peak approximately 20 minutes after ingestion [49]. However traces of THC can exist in the body for several days following use. There may have been a background level of cannabis in the system for some of the regular users taking part in the study and this must be taken into account when interpreting the results. However, the consequences produced from 're-dosing' during the cannabis moments are still valid due to the almost immediate effects of cannabis use.

ESM can be a demanding methodology and requires sustained attention and motivation to fill out diary entries. This may deter some individuals, and thereby result in a selection bias. In addition, like other ESM studies [50, 51] the participant sample size was relatively small and therefore may not generalize to all individuals with co-occurring cannabis use and BD. However a large number of data points were generated as ESM data has a hierarchical structure with the repeated participant observations (level one), nested within days (level two), nested within participants (level three).

Additionally, the majority of the sample was from a white British background and had a diagnosis of BD-I. It is therefore questionable how much the findings of this study may generalise to people from different ethnic minorities or other BD groups.

Finally, Henquet et al [20] used a study sample with individuals with a clinical diagnosis of a psychotic disorder and healthy controls. Both groups were frequent cannabis users (current use of at least 3 times per week). The results from the study were different for both groups, with cannabis use associated with a decrease in negative affect and an increase in hallucinatory experiences in the clinical group alone. The inclusion of a control group (individuals without a mental health diagnosis who regularly used cannabis) in this study may have provided insight into whether the findings of the study relate exclusively to those with a diagnosis of BD, compared to a non-clinical sample.

Clinical Implications

Overall results from the present study indicate that cannabis use can cause a range of psychological effects for individuals with BD, including an exacerbation of both manic and depressive symptoms. Co-occurring BD and substance abuse is highly prevalent [6, 52] and it is associated with worsened outcomes [5, 6, 7]. However intervention research for BD and substance abuse is in its infancy [53, 54, 55, 56] and demonstrates a limited evidence base [53]. The results from this study may help to inform future interventions.

Clients often find it difficult to reduce their substance intake and the literature suggests that some individuals perceive cannabis as a useful coping strategy in the management of their BD

symptoms. However results from this study may help to counter these positive expectations of their substance use. The findings suggest that cannabis is not being used to self-medicate changes in symptoms, within the context of daily life, and in fact it may be further complicating affective states. Services and clinicians need to be aware of the potential impact of using cannabis and able to inform clients of the risks. Alongside this it may be helpful for clinicians to offer alternative strategies to help clients cope with changes in BD symptoms, which may in turn increase an individual's confidence to reduce their substance intake.

Similar to Henquet et al's findings [20], the majority of participants in this study reported that they found the ESM diary a useful and reflective tool to monitor their mood and cannabis use. Anecdotally, a number of participants reported that tracking patterns of mood and cannabis use led them to question their substance use and in some cases reduce intake. ESM could provide an invaluable therapeutic tool, particularly with clients who are ambivalent about changing their drug use habits, providing insight into unhelpful patterns of behaviour, which may contribute towards the maintenance of their difficulties.

Conclusion

The findings from the study indicate that cannabis use is associated with a subsequent change in positive affect, depressive symptoms and manic symptoms over the course of daily life. No evidence for the use of cannabis to self-medicate minor fluctuations in negative affect or BD symptoms was revealed. Participants in the study were currently well and out of episode. Future research should explore whether the self-medication hypothesis is more relevant to individuals that are in the acute stages of depression or mania. This would be consistent with the broader self-medication hypothesis in BD where individuals have reported finding cannabis useful in the management of their symptoms [13, 14, 15].

Supporting Information

S1 Dataset.

(SAV)

Author Contributions

Conceived and designed the experiments: ET SJ CB. Performed the experiments: ET NB. Analyzed the data: ET LC. Contributed reagents/materials/analysis tools: ET SJ NB LC CB. Wrote the paper: ET SJ CB LC.

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To cite this article: Lester Grinspoon & James B. Bakalar (1998) The Use of Cannabis as a Mood Stabilizer in Bipolar Disorder: Anecdotal Evidence and the Need for Clinical Research, Journal of Psychoactive Drugs, 30:2, 171-177, DOI: [10.1080/02791072.1998.10399687](https://doi.org/10.1080/02791072.1998.10399687)

To link to this article: <http://dx.doi.org/10.1080/02791072.1998.10399687>



Published online: 06 Sep 2011.



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The Use of Cannabis as a Mood Stabilizer in Bipolar Disorder: Anecdotal Evidence and the Need for Clinical Research

Lester Grinspoon, M.D.* & James B. Bakalar**

Abstract—The authors present case histories indicating that a number of patients find cannabis (marihuana) useful in the treatment of their bipolar disorder. Some used it to treat mania, depression, or both. They stated that it was more effective than conventional drugs, or helped relieve the side effects of those drugs. One woman found that cannabis curbed her manic rages; she and her husband have worked to make it legally available as a medicine. Others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects. Another case illustrates the fact that medical cannabis users are in danger of arrest, especially when children are encouraged to inform on parents by some drug prevention programs. An analogy is drawn between the status of cannabis today and that of lithium in the early 1950s, when its effect on mania had been discovered but there were no controlled studies. In the case of cannabis, the law has made such studies almost impossible, and the only available evidence is anecdotal. The potential for cannabis as a treatment for bipolar disorder unfortunately can not be fully explored in the present social circumstances.

Keywords—bipolar, cannabis, depression, lithium, mania, marijuana

[EDITOR'S NOTE: The following article is based in part on materials that appear in the revised and expanded edition of the authors' book, *Marijuana, The Forbidden Medicine*, republished in 1997 by Yale University Press, New Haven and London. While the interviews have previously appeared in print, they provide a reference point for the authors' discussion of cannabis' potential role in the treatment of bipolar disorder as it appears in this theme issue. In their revised and expanded book, Grinspoon and Bakalar discuss a wide range of what they refer to as "Common Medical Uses" and "Less Common Medical Uses" for cannabis. The

former include treatment for the nausea and vomiting of cancer chemotherapy, glaucoma, epilepsy, the muscle spasms of multiple sclerosis, paraplegia and quadriplegia, the weight loss syndrome of AIDS, chronic pain, migraine, rheumatic diseases, pruritus, PMS, menstrual cramps and labor pains, depression and other mood disorders. The latter include treatment for asthma, insomnia, antimicrobial effects, topical anesthetic effects, antitumoral effects, dystonias, adult ADD, schizophrenia, systemic sclerosis, Chron's disease, diabetic gastroparesis, pseudotumor cerebri, tinnitus, violence, PTSD, phantom limb pain, alcoholism and other addictions, terminal illness and aging.]

*Associate Professor of Psychiatry, Department of Psychiatry, Harvard Medical School, Boston.

**Lecturer in Law, Department of Psychiatry, Harvard Medical School, Boston.

Please address correspondence and reprint requests to Lester Grinspoon, M.D., Harvard Medical School, 74 Fenwood Road, Boston, Massachusetts 02115.

In bipolar or manic-depressive disorder, major depression alternates with uncontrollable elation, or mania. Symptoms of depression include loss of interest and pleasure in life, sadness, irrational guilt, inability to concentrate,

appetite loss, lethargy, and chronic fatigue. Manic symptoms include sleeplessness, tirelessness (until exhaustion leads to a breakdown), and recklessly gregarious and expansive behavior, which sometimes turns to irritability, rage and paranoid delusions. Bipolar disorder is treated mainly with lithium salts and anticonvulsant drugs, which can have serious side effects. Thirty percent to 40% of patients with bipolar disorder are not consistently helped by or cannot tolerate standard medications. In the course of the authors' studies of the medical uses of cannabis (Grinspoon & Bakalar 1997), a number of sufferers were discovered who believed marijuana to be more effective than conventional anti-manic drugs, or who used it to relieve the side effects of lithium.

Our first account was written by a 47-year-old woman:

I was born on Friday, October 13, 1950, a few months before my father had his first serious bout with manic depression. My mother said he was taking valuable art objects they owned and throwing them down the trash chute in their New York apartment building.

I enjoyed my youth with a great deal of abandon. How much of this would be mood disorder I could not tell you. As a single person I didn't notice; I just rode the waves of emotional highs and lows and didn't think much about it. I was an old pro at this by the time I was 19 and met my husband. It was only through my association with him that I came to terms with my mood problems, although right before I met him I had checked myself in at a mental health clinic complaining that I sometimes felt unable to concentrate on one thing at a time.

I think I was 22 years old when my troubles cropped up again. At one point my husband and I went to see a psychologist. We talked about my mood swings and spells of nervousness, anger, and depression. The tiniest negative thing happening would cause long-lasting rage, very hard to quell. We told the psychologist of my father's history, even longer and grislier by then. He must have been in every state mental institution along the east coast. My grandmother, his mother, was wasting away by this time, losing her lifelong battle with chronic depression. I don't know much about her case except that she was chronically sad and starved herself to death after her husband passed away.

This man said my husband and I needed to lose weight; that was the extent of his advice. We did not see him much longer. By this time I was experiencing most of the symptoms I have today, although they have strengthened year by year. Sometimes I feel elated, exhilarated, with a great deal of energy. It sounds great, but you can get to be feeling so good that you scare the people around you, believe me! This is accompanied by light sleeping and nocturnal habits. I tend to become angry or aggressive when it is not appropriate, or just talk too loud. I often have a low self-image or feel sad. I sometimes have a hard time getting up to work, a heaviness that keeps me from moving. I get racing thoughts that make concentration hard. I have strong emotions that change rapidly. I tend to be physically clumsy. I develop unexplained skin rashes, and sometimes feel like I'm generating electricity and shooting it out my fingers and toes. My judgment is often poor.

It was in my early twenties that I first used cannabis for my condition. I had been exposed to it several times, the first

when I was quite young. My mother had taken me to a mental health center after my initial signs of trouble as a child. After a group therapy session there, some of the other kids took me riding and gave me a joint. Nothing at all happened, and I concluded it must be a mild drug.

When I was exposed to it later, I would actually choose it over alcohol because it didn't have such strong and negative effects on me. This is how I discovered that it was effective against most of my symptoms. Suppose I am in a fit of manic rage—the most destructive behavior of all. A few puffs of this herb and I can be calm. My husband and I have both noticed this; it is quite dramatic. One minute out of control in a mad rage over a meaningless detail, seemingly in need of a strait jacket, and somewhere, deep in my mind, asking myself why this is happening and why I can't get a handle on my own emotions. Then, within a few minutes, the time it takes to smoke a few pinches—why, I could even, after a round of apologies, laugh at myself!

But this herb is illegal and I have a strong desire to abide by the law. My father was having great success with a new drug, lithium carbonate. I saw my father's physician and he recommended that I try it. I took lithium for six months and experienced several adverse side effects: shaking, skin rashes, and loss of control over my speech. But I would still be taking it if it had worked for me as it did for my father. It literally restored his life. I had gotten worse, if anything.

The combination of lithium side effects and increased manic depressive symptoms drove me back to the use of cannabis. Some years later I tried to go without it again, this time because of increased social pressure against illegal drug use. It was a very difficult time for my family. Whenever I started to become manic, my husband and son would get scared and cower, triggering rage and making matters worse. When depression struck it was a black funk on our household. And I can tell you from the experience with my father that this can really destroy a family. After a while the knowledge that a little bit of marijuana would help me so much became irresistible. At first I tried eating cannabis, but soon returned to smoking because I could control the dose better.

I don't at all consider myself a drug abuser. I am doing what any rational person in my position would do. Cannabis does not cure my condition and over the years it has probably continued to worsen. But with judicious use of this medicine my life is fine. I can control things with this drug that seems so harmless compared to the others I've tried, including tranquilizers as well as lithium. I am constantly concerned that I will be cut off from my supply of marijuana or caught with it in my possession. I feel my sanity may depend on it. Cannabis lessens what is troubling me and returns me to a more normal state. Often I do not experience a "high" at all, just a return to normal.

This patient's husband bears witness to the usefulness of cannabis:

I've been mates with my full-blown manic-depressive (M-D) wife for 26 years. Her father was the classic, well-studied and well-written-about manic-depressive, and she's the one who inherited it. She's lovely, and as I've always truthfully told her, she has the perfect personality, blemished only by M-D.

I've always been smooth-sailing. Smoking marijuana only makes me sleepy. I never use it. She requires it, or, I

swear she'd be institutionalized just like her father. There wouldn't be any other way.

We've tried Marinol (dronabinol). It works for her too, but to get the same effect as marihuana she must take 10 mg about six times a day, which costs about \$65 a day. What's worse is that it takes forty-five minutes to engage and tapers off within two hours maximum. Timing of capsule ingestion must be exact or the symptoms can print through. Marihuana [smoked] lasts a little longer and is smoother, and, most importantly takes effect quickly.

What does marihuana do for my wife? It "recenters" her personality and her interaction with the immediate family moves back into a normal range—no highs, no lows, at least not the highs and lows that are abnormally extreme and that you can tell are from a crazy person with active M-D. Narcoleptic drugs really "zone" her out, like a temporary lobotomy in a medicine bottle. Marihuana never does that! It normalizes, that's all. If there's an overdose, which is rare, it's not dangerous and is very short.

Yesterday we went downtown (one and a half hour's drive one way). However, going several hours without the medicine can be quite calamitous. The worst kind of getting along badly ensued. That's the exact nature of M-D. You tear at your mate with unfounded suspicions, accusations, insane bitterness—enough to make you hate each other. It makes no sense. That's why it's crazy behavior. If you're lucky, like my wife, your mate understands and gets you home right away to have a smoke. It used to be that you could take trips, but the police have cracked down so hard that you don't dare smoke a joint in the car.

I can bear witness to the probability of a near normal life situation for a manic-depressive if they've got good marihuana, a lifestyle that allows one to be home nearly always, and an understanding partner.

Here is the account of another woman with bipolar disorder who finds cannabis more useful than conventional medications:

I am a 35-year-old woman with severe manic depression. When I was growing up I was hypersensitive, cried all the time, and fought with my brothers and sister. My parents always said they had to handle me with kid gloves. I had more energy than most and used it to the hilt. I was an agile gymnast and one of the fastest swimmers in my school. I was also at the top of my class in algebra and good at art and creative writing. I used to stay awake at night and dream up stories.

Around age 14 my mood swings began to get more intense. I was agitated, restless, and constantly fighting at home. I lay awake at night and lost a lot of weight. Eventually I snapped and was sent to a mental hospital, where I was diagnosed as having manic-depressive disorder. They put me on lithium and told me I would have to take it the rest of my life. But lithium made me lethargic. I had trouble communicating and lost all my animation and creativity. Eventually I quit taking it. Recently I have also tried Tegretol [carbamazepine] and Depakote [valproic acid], neither of which helped. Tegretol started a manic episode, and Depakote had some very bad side effects. I'd like to find something else, but I don't have health insurance or the money to spend trying out new medications.

Since the age of 14 I have had manic episodes regularly about once every six months. It would always start with

not being able to sleep or eat. After two weeks I would just break down and seem to trip out into another world. Usually I ended up in a mental hospital.

I smoked marihuana for the first time in high school and couldn't believe how good it made me feel. My normally chaotic emotions subsided and I had a sudden sense of calm, peace, and well-being. My perceptions of others and life changed dramatically. The world no longer seemed hostile but more within my control. I could sleep easily and actually had cravings for food. There were practically no side effects. When I had enough marihuana I would just naturally stop, because once you've gotten a certain effect you really don't want any more.

Only another manic-depressive using marihuana could possibly know how much this has changed the quality of my life. Although they don't know it, my family actually likes me better when I'm stoned than when I'm taking lithium or not taking anything. When I'm stoned they can predict my moods and actually get close to me. But I can't tell my family or the doctors because it's illegal. I have to live a double life to get along.

I've often tried to quit marihuana, but I have a manic episode every time. Last year I decided I could control my emotional ups and downs without marihuana, but it led to one of the worst episodes I've ever experienced. I had been having trouble sleeping as usual. I began to get super clear vision that a disastrous earthquake was going to hit Los Angeles. I was feeling so good I was sure I was right. Soon I had my roommate convinced that we didn't have much time and would have to buy as many supplies as possible and then leave. We thought that after the quake the New World Order would be implemented and everyone would have to take the number that Revelations talks about in the Bible. We planned to go to El Salvador, where her family lives, and hide out for the next three and a half years. Crazy! But I really believed it. I maxed out all my credit cards, quit my job, and packed up all my things, including disguises I thought we were going to need. Eventually I had to return home with no job and major bills.

I knew then and there that I would have to go back on marihuana. It's been seven months now since I resumed smoking marihuana, and I don't know what else to do. I have to choose between obeying the law and staying sick or breaking the law and being well.

J.P. is a 45-year-old health professional and the mother of a 20-year-old son:

In late 1994 and early 1995 my son Michael, age 18, began to go out of control. He was unable to sleep, attend school, or function in a normal fashion. He was running around non-stop, acting on impulse without any sense of normal judgment. He was in serious danger of accidentally harming himself or others. There was no way to reason with him, because he was unable to think or listen long enough to understand what you were trying to say. He had become a human time-bomb.

Then, on February 14, 1995, he had a full-blown psychotic manic episode and refused treatment. I had to petition a court to commit him to a psychiatric hospital in Portland, Maine, where he was given a diagnosis of manic-depressive disorder. Both Michael's father and my grandmother suffered from the same disorder, which is now called bipolar disorder.

During his nine days in the hospital (the time allotted by my insurance company) Michael was given lithium and Trilafon [perphenazine]. We were told that he would need lithium for the rest of his life. They explained that it worked very well in 60% of people with this disorder.

We returned home, and for the first month or two, the mania seemed to have ended. At the end of the second month the Trilafon was discontinued, but Michael was still taking a high dose of lithium. At that point he developed a rash on his neck and chest; he also had dark circles under his eyes, and he was incoherent most of the time. The lithium level in his blood was exactly where the doctor wanted it, but now he was acting like an Alzheimer's patient. He couldn't read or comprehend a paragraph, let alone finish school. He was detached from his surroundings and himself. There was no emotional content left in him. He was becoming unrecognizable. He had always been very much like [comedian] Robin Williams in personality and extremely athletic—a skier, football player, and weight lifter. It was heartbreaking to watch him lose himself in a medicated stupor. I became convinced that lithium did not eliminate the disease but instead was drowning his brain so the symptoms could not be activated. I could still see tiny mood swings and moments of complete restlessness, but in a body that was unable to become hypomanic.

Michael decided to cut his lithium in half. I knew this would be dangerous but I agreed that something had to be done. Soon he was more himself, laughing and talking and almost back among the living. Then he started to become more hypomanic, and I knew we were headed for trouble. He was back to the energy level of someone on high doses of speed, and this lasted for months. He was running through life like a high-bred stallion, while I was gathering everything ever written on manic-depressive disorder.

Then one day he came home and was perfectly normal in every respect. I thought that maybe he was in remission because the disease is known to do that, and I was thrilled at the possibility. Later that night he was back to full speed ahead, and all hope sank within me. This continued as the weeks passed. There would be times when he was perfectly normal, but only for short intervals. I could not figure it out. I started to chart his sleep pattern, his food intake, the kinds of foods, what chemicals he was subjecting himself to, and so on. Finally one day I discovered that he was smoking pot. Of course I freaked out. We talked about it at length and he told me point blank, "I only feel normal when I smoke a joint." By this time I was ready to blame the disease on his pot smoking. I was totally irrational about this. Michael and I fought constantly for a month about it. Finally he asked me to research cannabis and let him know what I found. I figured I would be able to find enough damaging information to put the subject to rest. The next week was my week of discovery. Not only could I not find what I was looking for, but I became convinced that there was no permanent damage, and that cannabis was actually helpful for people with mood disorders.

I went on-line on the computer to talk to other people suffering from bipolar disorder, and I was overwhelmed by first-person stories of the benefits that others had found.

The hardest part of this entire thing was rearranging my value system. I was raised to be a law-abiding citizen. Although I grew up in the sixties and had tried pot and inhaled, I was never a regular user because it was illegal. I raised Mike right. He was taught to respect elders, do what you are supposed to do, and above all follow the law.

It is hard enough to live with an 18 year old during a naturally rebellious time, but to be forced to participate in an illegal activity is the absolute worst scenario. But that is exactly what I'm doing. Mike has been smoking pot for two months now. He does not smoke daily, but when the mania begins he smokes and within five minutes he is fine. He never appears to be "high," just happy and relaxed. We don't have to deal with mood swings anymore. He can work on his home-schooling program, and I don't doubt that he will finish by the end of summer. He has been repairing lobster traps with a friend and will be lobstering six days a week by the end of April.

At this point I expect to be arrested some day, because if Mike gets arrested, they will have to take me right along with him. I plan to grow a plant this summer for his use. I know I could end up in jail, but I also know that without some kind of medication that works, my son could end up in jail, institutionalized, or dead. What choice do I have?

Another account of cannabis use by a person with bipolar disorder emphasizes the reduction of lithium side effects:

I am 29 years old, born and raised in North Carolina. My academic background is in English literature, computer science, and law; I now work as a technology consultant and writer, although I am contemplating returning to graduate school. I am divorced. I am reasonably active in my community, though work takes much of my time these days.

I was first diagnosed with bipolar disorder about five years ago, when I was in law school (a psychiatrist also tentatively ventured this diagnosis during my undergraduate years), but I suspect that I have had a mood disorder for most of my life. I was certainly clinically depressed as early as age nine, and my first hypomanic episode occurred at 17. There is also a family history of mood disorders, especially on my mother's side. All three of her brothers had "mercurial" personalities, and they all experienced tremendous successes and notable failures in business. Their extravagance and outgoing personalities resemble my behavior while manic or hypomanic. Although none of them was formally diagnosed with a mood disorder, both my parents have been treated for clinical depression.

Before I was diagnosed and found the right treatment, I had the typical symptoms of bipolar disorder. During depressive phases I became withdrawn, uncommunicative, and preoccupied with suicide. I found it nearly impossible to function in school or at work. During hypomanic or manic phases I spent freely, traveled all over the country (and world), made poor personal and business decisions, engaged in risky sexual behavior, and so forth. The illness has caused me a great deal of personal pain as well as financial woes. I separated from my wife (who eventually divorced me) the summer before I was diagnosed. I've lost jobs, ruined friendships, and alienated members of my family. Fortunately, much of this damage has been repaired with time and understanding. I thank God that my ruined credit rating is the only apparent lasting harm.

Thanks to lithium and sensible therapy, including the judicious use of cannabis, I have been relatively stable and sane for the past three years, although my sleep is often disturbed and I still have (very much milder) hypomania and depression in much the same cyclic pattern as before.

I first used cannabis in my freshman year of college (1984). I preferred it to alcohol as an intoxicant, and used it a few times a week, almost always by smoking (I still prefer to take it that way). In retrospect, it seems clear to me that I was medicating myself for bipolar disorder even then. When depressed and anxious, I found that cannabis was soothing and enhanced my ability to enjoy life. When I was in a manic phase, it relaxed me and helped me get to sleep. I often felt as though I had so much energy inside me that I would jump out of my skin; the cannabis helped tremendously with that. But there was a downside. Manics have a big problem with impulse control, and cannabis seemed to exacerbate it. ("Drive to Canada? Great idea. Let's go!") It also ratcheted up my already overactive libido a notch or two, which wasn't the healthiest thing in the world.

When I was diagnosed and began treatment with lithium, I got almost immediate relief, but I also suffered from nausea, pounding headaches, hand tremors, and excess production of saliva. A friend suggested that I try getting high, reasoning that if cannabis helped chemotherapy patients deal with their nausea and discomfort, it might help me too. My doctor thought the idea was absurd but admitted that it would be safe to take cannabis together with lithium. So I tried it, and the results were remarkable. The hand tremors subsided, the headaches vanished, and the saliva factory resumed normal production levels. All I needed was one or two puffs on a marihuana cigarette. When lithium side effects get bad, the availability of cannabis has been an absolute godsend. It is also nice to be able to use cannabis as an intoxicant, knowing that, unlike the combination of lithium and alcohol, it cannot damage my kidneys.

Every one of the many thousands of Americans who use marihuana as a medicine runs a risk of being arrested. They have to worry about financial ruin, the loss of their careers, and forfeiture of their automobiles and homes. Some have an additional burden because mandatory school drug programs and Parents for a Drug-Free America advertisements have given their children an exaggerated idea of the dangers of using marihuana. Many of these children become concerned about the health and well-being of their marihuana-using parents. A few of those parents have been arrested because their worried children informed on them to the police officers who serve as instructors in the popular school drug program known as Drug Abuse Resistance Education (DARE).

The following accounts are by a 40-year-old software engineer and his 37-year-old wife, who suffers from bipolar disorder. He speaks first:

My wife and I and our two boys live in Tyngsboro, Massachusetts. My wife was given a diagnosis of bipolar disorder in 1982 and has been taking lithium since 1992. She also uses marihuana for her symptoms. She has had six psychiatrists in the past 14 years and has been interviewed by many more. I have always told them that she uses marihuana regularly, and not one of them has told her to stop. They do not even seem to care or pay attention.

I posted a question about this to the alt.support.depression.manic newsgroup on the Internet. I asked whether doctors knew something about marihuana but could

not recommend it because of its illegality. The responses were varied, but most people who were manic-depressive said marihuana helped them, and one said that some doctors considered it effective in controlling mood disorders.

My wife functions much better when she uses marihuana. When she is hypomanic, it relaxes her, helps her sleep, and slows her speech down. When she is depressed and would otherwise lie in bed all day, the marihuana makes her more active. When she runs out of marihuana and can't get more, she becomes more irritable and hard to live with. Lithium is also effective, but it doesn't always keep her in control.

Our dilemma is that our 13 year old has been through the DARE program and has learned about the evils of drugs and alcohol. He opposes all substance use, legal or illegal—and I want it that way. But he knows that my wife uses marihuana and it "eats" at him, although he also knows about her illness and how marihuana helps. Understandably, all this confuses him.

I believe that marihuana could help some people if it were made available as a prescription medicine. Certainly there are other health and social issues involved, and I can't decide what would be right for the country as a whole. All I know is that in this family it has relieved us all of much suffering.

Now his wife:

I am 37, and I have been using marihuana for 20 years. I was diagnosed bipolar in 1982. I take lithium and Wellbutrin [bupropion], although I dislike these drugs. I've gained about 40 pounds since I started taking lithium, but otherwise there are no side effects.

My 13-year-old son knows about my illness. He has also known about my marihuana smoking for about five years. He realized what I was doing after he participated in the DARE program in school. It bothers me when he comes home and says they talked about drugs and he was thinking that his mother is "one of them." He doesn't want anyone to know his mother is a "druggie," and until now we've kept it as our secret. I don't think he would tell anyone, but I'm still afraid something might get out. Sometimes these programs use tricks to get kids to inform on their friends and relatives. They say, "If you really care about this person, the only way you can help them is to report them." My husband has talked to him about it. He has explained that lithium and the other medications I'm taking are drugs. He also explained that many legal drugs are far more dangerous than marihuana and that no one has ever died from using marihuana. But my son insists that if it is illegal, then it is wrong. This bothers me so much that I have considered stopping.

The trouble is that at times when I feel tired and run-down, just a couple puffs of marihuana bring me back to life. Sometimes I think it brings me to a level of normalcy that everyone else achieves naturally. At other times, when everything seems to be going like a whirlwind around me and I can't keep track of what I'm thinking about or saying or feeling, the marihuana just seems to slow the world down a bit. When I have trouble sleeping, it helps zonk me out, but if I have trouble waking up it brings me to life. I don't like being thought of as a "drug-abusing mother," but I actually think I'm a better mom when I'm feeling in control because of marihuana.

In some ways cannabis today is in a position analogous to that of lithium in 1949, when J. F. J. Cade, after observing its sedative effect on guinea pigs, administered it to patients suffering from "chronic and recurrent mania." His seminal paper, "Lithium Salts in the Treatment of Psychotic Excitement," presented ten one-paragraph case histories, and this compelling anecdotal evidence attracted the attention of psychiatrists around the world because there was no adequate treatment for bipolar disorder. In his paper Cade (1949) mentioned the need for "controlled observation[s] of a sufficient number of treated and untreated patients." In 1951, Noack and Trautner followed up by reporting on the treatment of another 30 patients with "mania alone." But they pointed out that not all patients improved, that many discontinued the treatment, and that "it does not appear to be justified to accept the lithium treatment of mania as invariably safe." (Noack & Trautner 1951).

In 1954, Schou and colleagues published a controlled study in which they alternated lithium and a placebo at two-week intervals. Lithium was clearly beneficial for 12 patients; 15 showed improvement that was "not as clear-cut," and three did not improve at all. Schou and his colleagues found it "rather astonishing that [lithium's success] has failed to arouse greater general interest among psychiatrists." One explanation they offered was its low therapeutic ratio. Another explanation was "the difficulties encountered in attempts to convey to others in a quantitative manner . . . the effect of a new psychiatric therapy," i.e. to move beyond anecdotal data to controlled studies (Schou et al. 1954). But there was an even more compelling reason for the delay in lithium's acceptance in the United States. In this country, drugs are introduced by pharmaceutical companies which invest in the studies necessary for official acceptance. They do this because they receive a patent (in the 1950s, for 17 years) on the new drug which allows them to recoup their investment. Lithium salts, of course, could not be patented.

Similar obstacles face the medical use of cannabis today. Lithium had a reputation for toxicity that grew out of its use as a salt substitute for cardiac patients in the 1940s. There were a number of deaths before its dangers were fully appreciated, and today blood levels are carefully monitored. Because of its nonmedical use, cannabis also has a reputation for toxicity, in this case undeserved. Lithium was unpatentable, and so is cannabis. Finally, like the evidence for lithium in 1949, the evidence for the therapeutic value of cannabis in bipolar disorder today is anecdotal. Although it has been repeatedly considered as a treatment for affective disorders in the Western medical literature since 1845, when Jacques-Joseph Moreau de Tours (1857) recommended it for melancholia, there is little in the medical literature on the use of cannabis as a mood stabilizer (see Parker & Wrigley 1950; Pond 1948; Stockings 1947).

Today drugs must undergo rigorous, expensive, and time-consuming tests to win approval by the Food and Drug

Administration (FDA) for marketing as medicines. The purpose of the testing is to protect the consumer by establishing both safety and efficacy. First the drug's safety (or rather limited toxicity) is established through animal and then human experiments. Next, double-blind controlled studies are conducted to determine whether the drug has more than a placebo effect and is at least as useful as an available drug. As the difference between drug and placebo may be small, large numbers of patients are often needed in these studies for a statistically significant effect. Because no drug is completely safe (nontoxic) or always efficacious, a drug approved by the FDA has presumably satisfied a risk-benefit analysis. When physicians prescribe for individual patients they conduct an informal analysis of a similar kind, taking into account not just the drug's overall safety and efficacy but its risks and benefits for a given patient and a given condition. The formal drug approval procedures help to provide physicians with the information they need to make this analysis.

But devotion to formal procedures may have caused us to undervalue anecdotal evidence. Regulators today are willing to accept the experience of physicians and patients as evidence of adverse effects but not as evidence of therapeutic effects (Lasagna 1985). Yet case histories and clinical experience are the source of much of our knowledge of synthetic medicines as well as plant derivatives. Controlled experiments were not needed to recognize the therapeutic potential of chloral hydrate, barbiturates, aspirin, curare, insulin, or penicillin. More recently, the uses of propranolol for angina and hypertension, diazepam for status epilepticus, and imipramine for childhood enuresis were discovered in the same way, although these drugs were originally approved by regulators for other purposes.

A related source of evidence is the experimental method known as the "N of 1" clinical trial or single-patient randomized trial. This is the kind of experiment used by Schou and his colleagues (1954), in which active and placebo treatments are administered in alternation or succession to a patient. The method is often used when large-scale controlled studies are impossible or inappropriate because the disorder is rare, the patient is atypical, or the response to treatment is idiosyncratic. Several patients the authors have encountered carried out somewhat similar experiments on themselves. They alternated periods of cannabis use with periods of no use and discovered that cannabis was effective.

The familiar deficiency of anecdotal evidence is the risk of counting successes and ignoring failures. If many people suffering from clinical depression take, say, St. John's Wort after unsuccessful treatment with conventional antidepressants and a few recover, those few stand out and come to attention. Bipolar disorder is a cyclical condition, so it is essential to avoid confusing natural remission with drug-induced improvement. At present we do not know how many patients with bipolar disorder would benefit

from cannabis. The promising anecdotal evidence points to the need for more systematic clinical investigation, just as it did 50 years ago in the case of lithium.

Thousands of years of widespread use as well as recent research designed to discover toxic effects have made it clear that cannabis is an unusually safe drug. In fact, its long-term safety is better established than that of St. John's Wort. Yet unlike St. John's Wort, cannabis would be subject to government regulations that demand further time-consuming and unnecessary safety tests. The classi-

fication of cannabis as a Schedule I drug creates further obstacles to clinical research. But given the disinterest of pharmaceutical companies, there is no immediate prospect of such studies being funded even if the political obstacles are removed. We are left with the tantalizing possibility that cannabis (or one or more of its constituent cannabinoids) is useful in the treatment of bipolar disorder and the sad knowledge that in the present circumstances little can be done to explore that potential.

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RESEARCH ARTICLE

Joint Effects: A Pilot Investigation of the Impact of Bipolar Disorder and Marijuana Use on Cognitive Function and Mood

Kelly A. Sagar^{1,2}, M. Kathryn Dahlgren^{1,3}, Megan T. Racine^{1‡}, Meredith W. Dreman^{1‡}, David P. Olson^{1,2}, Staci A. Gruber^{1,2}*

1 Cognitive and Clinical Neuroimaging Core, McLean Imaging Center, McLean Hospital, Belmont, Massachusetts, United States of America, **2** Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, United States of America, **3** Department of Psychology, Tufts University, Medford, Massachusetts, United States of America

☞ These authors contributed equally to this work.

‡ These authors also contributed equally to this work.

* gruber@mclean.harvard.edu



OPEN ACCESS

Citation: Sagar KA, Dahlgren MK, Racine MT, Dreman MW, Olson DP, Gruber SA (2016) Joint Effects: A Pilot Investigation of the Impact of Bipolar Disorder and Marijuana Use on Cognitive Function and Mood. PLoS ONE 11(6): e0157060. doi:10.1371/journal.pone.0157060

Editor: Kenji Hashimoto, Chiba University Center for Forensic Mental Health, JAPAN

Received: February 24, 2016

Accepted: May 5, 2016

Published: June 8, 2016

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: Support for this project was provided by the National Institute of Drug Abuse (<https://www.drugabuse.gov/>) R21 DA21241-2 and 1R01-DA032646 awarded to SG and by generous funds donated by the Jim and Pat Poitras Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Marijuana is the most widely used illicit substance in those diagnosed with bipolar I disorder. However, there is conflicting evidence as to whether marijuana may alleviate or exacerbate mood symptomatology. **As bipolar disorder and marijuana use are individually associated with cognitive impairment, it also remains unclear whether there is an additive effect on cognition when bipolar patients use marijuana.** The current study aimed to determine the impact of marijuana on mood in bipolar patients and to examine whether marijuana confers an additional negative impact on cognitive function. Twelve patients with bipolar disorder who smoke marijuana (MJBP), 18 bipolar patients who do not smoke (BP), 23 marijuana smokers without other Axis 1 pathology (MJ), and 21 healthy controls (HC) completed a neuropsychological battery. Further, using ecological momentary assessment, participants rated their mood three times daily as well as after each instance of marijuana use over a four-week period. Results revealed that although the MJ, BP, and MJBP groups each exhibited some degree of cognitive impairment relative to HCs, no significant differences between the BP and MJBP groups were apparent, providing no evidence of an additive negative impact of BPD and MJ use on cognition. Additionally, ecological momentary assessment analyses indicated alleviation of mood symptoms in the MJBP group after marijuana use; MJBP participants experienced a substantial decrease in a composite measure of mood symptoms. Findings suggest that for some bipolar patients, marijuana may result in partial alleviation of clinical symptoms. Moreover, this improvement is not at the expense of additional cognitive impairment.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

Bipolar disorder (BPD), considered one of the most debilitating mood disorders, is the sixth leading cause of disability in the world according to the World Health Organization. In those affected, BPD is often a significant source of distress and burden on relatives and caregivers [1]. Further, among Axis I pathologies, BPD carries the highest risk of substance use comorbidity, which can complicate the course of illness and impact treatment outcomes. In fact, patients with co-occurring BPD and substance use often experience poor treatment response, relapse of mood symptoms, psychosocial difficulties, and reduced treatment compliance [2–4]. Despite evidence that suggests substance use is linked to poorer outcomes, some studies have also shown that BPD patients engage in substance use to improve clinical symptoms. Bolton and colleagues [5] found that almost a quarter of those with mood disorders used alcohol or drugs to relieve symptoms, with the highest rates of self-medication seen in bipolar I disorder. In another study, the authors found that specifically amongst BPD patients who use substances, 79% engaged in drug use *specifically* to improve mood symptoms [6].

Marijuana (MJ) is the most commonly used illicit substance in the US; this statistic also holds true among those diagnosed with BPD [7]. Moreover, rates of MJ use disorders in BPD patients have been found to equal or exceed those of alcohol abuse or dependence, particularly in younger patients [8]. Research has also shown that 20–50% of patients report some form of MJ-related problems [9]. In those who endorse MJ-related problems, 63.7% reported disability, as compared to only 44.5% of those not meeting criteria for MJ use disorders, supporting previous findings that patients with BPD who engage in MJ use exhibit reduced compliance, higher levels of illness severity, and increased likelihood to attempt suicide [4, 7–8, 10–12].

While these studies appear to suggest that MJ use *results* in negative outcomes, a specific cause-and-effect relationship has yet to be determined. Although many studies have reported that MJ use precedes the onset of BPD [13–16], it remains unclear whether MJ use contributes to the pathogenesis of the disorder, or if it is used to address symptomatology, perhaps as a form of premorbid self-medication [17–19], especially if traditional pharmacotherapeutic regimens are ineffective at symptom alleviation. Others have also reported that individuals with higher levels of illness severity may be at risk for MJ use *after* the onset of the disorder [20]. Further research is needed to clarify the relationship between MJ use and the manifestation of BPD symptoms. Despite claims of negative outcomes associated with MJ use, whether patients' view MJ use as successful in symptom improvement is rarely assessed. In a single study of BPD patients, Weiss et al. [21] reported that nearly all patients initiated substance use as the *result* of one bipolar symptom, and the majority of patients reported improvement that was attributable to substance use for at least one symptom. Further, in a review of anecdotal reports of MJ use among BPD patients, the authors concluded that MJ was not utilized for the “high” sought out by recreational users, which may suggest that the effects of MJ are unique in sub-euphoric doses [22]. Regardless of the motive for use, the fact remains that MJ use is common in patients with BPD. As noted above, patients with BPD who use MJ have been shown to have higher illness severity and poorer outcome, yet report subjective improvement in symptoms after using MJ, suggestive of a complex relationship between MJ and mood [23]. Taken together, these data provide evidence that some patients with BPD may derive a clinical benefit from using MJ and highlight the importance of understanding the effects of MJ on mood symptomatology in those diagnosed with affective disorders.

Ecological Momentary Assessment (EMA), utilized in the current study, allows for the investigation of real-time assessment of mood and related symptoms as well as repeated collection of real-time data in participants' natural environment [24–25]. While most symptom assessments and diagnostic tools in both research and clinical settings rely on retrospective

recall of emotions and symptomatology using interviews and self-report questionnaires, EMA data is collected in naturalistic, real-world contexts and therefore offers improved ecological validity over traditional, retrospective methods. In fact, retrospective reports of mood have been shown to have a bias towards negative mood states such as anxiety, depression, and helplessness [26]. Collecting data in real-time with EMA reduces error bias from retrospective assessment and limits the effects of recall bias and generalization of symptoms over a period of time (Shiffman et al., 2008). Additionally, in a review article assessing the contribution of EMA on psychopathology research, Myin-Germeys and colleagues [27] suggest that symptoms in psychiatric disorders are dynamic and can meaningfully fluctuate through the course of the day. Thus, the increased ecological validity of EMA tools can provide better insight into the phenomenology and etiology of psychopathology than retrospective techniques. Better understanding of the development, maintenance, and progression of symptoms may lead to improved models of these disorders and help inform future treatment strategies [27].

Given a growing body of research indicating cognitive deficits associated with MJ use, it is also important to explore the impact of MJ across various cognitive domains. Interestingly, MJ users (without Axis I pathology) and BPD patients (who do not necessarily smoke MJ) have been shown to exhibit similar cognitive deficits. MJ use has been linked to impairments across a wide range of areas, including attention [28], memory [29–31], IQ [32–34], and executive function [35–37]. Similarly, BPD patients often evidence cognitive deficits across multiple overlapping domains; in two meta-analyses of euthymic BPD patients [38–39], the authors note marked impairment relative to healthy controls on measures of executive function, verbal memory, and attention. Despite the fact that MJ use and a diagnosis of BPD are both individually related to cognitive deficits, two studies examining neurocognitive function in MJ-smoking patients with BPD report surprising outcomes. Both Ringen et al. [40] and Braga, Burdick, DeRosse, and Malhotra [41] reported a *positive* association between neuropsychological functioning and MJ use in BPD patients, perhaps suggestive of a unique relationship between BPD and MJ use. Specifically, Ringen and colleagues [40] examined a variety of cognitive domains, including psychomotor speed, attention, working memory, executive functioning, and verbal learning. Overall, BPD patients who used MJ demonstrated better performance than patients who did *not* use MJ, although statistically significant results were only observed on tests of executive function. Similarly, Braga et al. [41] reported neurocognitive advantages in MJ-smoking BPD patients, relative to a non-smoking BPD group, spanning several domains, including executive function (Trails B) as well as attention and working memory. These results suggest that despite a more severe clinical course, BPD patients who use MJ may demonstrate a cognitive advantage relative to patients without a history of MJ use, underscoring the need for additional investigation.

Through EMA and a comprehensive neuropsychological battery, the current study aimed to clarify the relationship between acute MJ use and mood symptoms as well as cognitive function in patients with BPD. In order to accurately assess the impact of MJ use, BPD diagnosis, and the additive effects of both MJ use and BPD, we utilized a four-group study design enrolling healthy control subjects without MJ use or Axis I disorders (HC), MJ smokers without other Axis I disorders (MJ), individuals diagnosed with BPD without a history of MJ use (BP), and those diagnosed with BPD who currently used MJ (MJBP). We expected, in line with previous research, that the BP and MJBP groups would have more severely affected mood overall relative to the HC group. However, we further hypothesized that the MJBP group would experience significant mood improvement secondary to MJ use. In addition, although previous studies have shown that MJ use is related to cognitive deficits, there is a relative paucity of literature focused on the association between MJ use and cognitive function in patients with BPD. Therefore, the current study also aimed to determine whether MJ use has a differential effect

on cognitive performance in pure MJ smokers, BPD patients who smoke MJ (MJBP), and BPD patients who do not use MJ (BP).

Materials and Methods

Prior to participation, study procedures were thoroughly explained. All participants were also required to read and sign an informed consent form, a document that describes the procedures, risks, benefits, and voluntary nature of the study. This study and all study procedures were approved by the McLean Hospital Institutional Review Board.

Participants

As part of a larger study conducted between 2008 and 2014, 21 healthy control subjects (HC), 23 MJ smokers without other Axis 1 pathology (MJ), 18 individuals with bipolar I disorder who do not smoke MJ (BP), and 12 individuals diagnosed with bipolar I disorder who smoke MJ (MJBP), were enrolled and completed neuropsychological assessments. A subset of these participants also completed daily EMA assessments over the course of four weeks to assess mood.

Participants were not enrolled in the current study if they met criteria for any *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) Axis I pathology (with the exception of bipolar I disorder in the BPD groups, and MJ abuse/dependence in the MJ-smoking groups), as assessed by the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P) [42]. Individuals were also excluded if they reported a neurological disorder or significant medical problems, significant head injury with loss of consciousness, or were non-native English speakers (as necessitated by the cognitive assessment battery). Further, no participant was enrolled if they reported more than 15 lifetime uses of any illicit drugs (except MJ for the smoking groups) or recreational use of prescription or over-the-counter (OTC) medications, or had received electroconvulsive therapy.

Subjects enrolled in the MJ and MJBP groups were all well-characterized as chronic MJ smokers who reported smoking a minimum of 2,500 times in their lives, used MJ at least four out of the last seven days and tested positive for urinary cannabinoids. In order to ensure that cognitive test results were not affected by acute intoxication, all participants were also required to abstain from MJ use for at least twelve hours prior to study visits. Upon arrival, all individuals were required to provide a urine sample and, to ensure adherence to the twelve-hour abstinence requirement, were led to believe that this sample could be used to detect use within this time frame. This method has previously been used by our laboratory with success [36, 43–44]. Subjects were assessed for most recent use and any who violated the abstinence schedule or who appeared even vaguely intoxicated were rescheduled for a later date. An aliquot of the urine sample was sent to an outside laboratory for quantification of urinary cannabinoid concentration via gas chromatography–mass spectrometry during the initial and final study visit. Urinary THC levels were averaged across the two study visits.

Study Design and Measures

After completing diagnostic assessments, subjects who met inclusion criteria were enrolled in the four-week study, which contained a baseline visit and four weekly check-in visits. This study employed a combination Time-Based EMA design and Event-Based Monitoring [24–25]. The Time-Based EMA employed an alarm schedule, which alerted participants to complete three rating sessions per day. Each subject pre-selected three times throughout the day (at least five hours apart), which were tailored to his/her typical daily schedules, to rate their mood. In Event-Based Monitoring, EMA measures are triggered by the occurrence of a specific

event. For this study, participants were instructed to complete rating scales as soon as possible after MJ use in order to assess the acute impact of MJ on mood.

At the end of their initial screening study visit, all enrolled participants were issued a Palm Pilot (Palm Tungsten T5 PalmOne PDA) and instructed to use the device to rate their mood three times daily over the course of the four-week study. All individuals rated their mood using a custom-designed application, which contained electronic versions of several clinical rating scales: the Profile of Mood States (POMS) [45], which yields subscores for vigor, anger, confusion, tension, fatigue, depression, and a composite score for total mood disturbance (TMD); the Hamilton Anxiety Rating Scale (HAM-A) [46]; Montgomery-Asberg Depression Rating Scale (MADRS) [47]; and the Young Mania Rating Scale (YMRS) [48]. Participants who smoked MJ were also asked to use the device to record episodes of MJ use to allow for the calculation of pre- and post-MJ use mood changes. More specifically, for each episode of MJ use, participants recorded the amount (in grams), frequency, and mode of MJ use (bong, bowl, joint, etc.). Date and time were automatically recorded at the completion of each scale in order to assist with accurate pre- and post-smoking determinations. However, participants were also given the option to adjust the time of last MJ use when completing post-use ratings. Only ratings identified as being completed within four hours of MJ use were categorized as post-MJ use and used for analysis. To ensure that participants were not arbitrarily answering clinical rating questions, “quality control” questions were interspersed throughout the scales, with such questions such as “who is the current US president?” and “how thoughtfully are you answering these questions?”

In order to establish an estimate of overall intellectual functioning, participants completed the Wechsler Abbreviated Scale of Intelligence (WASI) [49]. In addition, all individuals enrolled also completed a neuropsychological battery designed to assay a variety of cognitive domains. Neuropsychological assessments were typically completed by the end of the first check-in visit, and consisted of a number of measures including the Wisconsin Card Sorting Test (WCST), Trail Making Test, Stroop Color Word Test, the Controlled Oral Word Association Test (COWAT), and Digit Span, which served as direct measures of executive function. The WCST assesses the ability to form abstract concepts, shift and maintain set, and utilize feedback, and is considered a gold-standard measure of executive function [50–51]. The Trail Making Test is comprised of two parts; while Trails A measures visual scanning and psychomotor speed, Trails B serves as a measure of cognitive set-shifting and attention [51]. The Stroop measures the ability to establish competing response tendencies, inhibit inappropriate responses, and resist interference [52]. The COWAT consists of two parts and serves as a measure of phonemic verbal fluency and executive function (participants must generate words starting with the specific letters F, A, and S) as well as verbal memory function (participants are required to generate words from a specific semantic category, in this case “Animals”) [53–54]. The Digit Span subtest from the Wechsler Adult Intelligence Scale—Revised (WAIS-R), requires subjects to recall increasingly longer strings of numbers in forward and then backward order, and reflects attention, working memory and executive functioning [55–56].

Study participants also completed additional cognitive measures, including the California Verbal Learning Test (CVLT), Rey-Osterrieth Complex Figure Test (ROCF), and Hooper Visual Organization Test (HVOT). The CVLT-II requires subjects to learn an orally presented list of words across five trials to assess verbal learning [57]. Errors and clustering strategies (i.e., grouping list items by category) are also documented to assess efficiency of learning. Further, the CVLT incorporates a delay trial, in which individuals are required to remember the list of words after a 20-minute delay in order to assess verbal memory. The ROCF assesses visual-spatial organization as well as visual memory and requires individuals to copy a complex figure and then draw it from memory both immediately and after a twenty-minute delay [51]. Finally,

the HVOT, a measure of visuoperception, requires participants to name objects in drawings that have been “cut” into pieces [58].

In addition, study participants completed the Fagerström Test for Nicotine Dependence (FTND) [59] in order to assess current level of nicotine use and level of dependence. The Addiction Severity Index (ASI) [60] was administered to calculate days of alcohol use within the past month. In order to assess average frequency and magnitude of MJ use, a modified timeline follow-back procedure [61] was utilized at weekly study visits, with a specific focus on the past week of use. Participants were asked to report the number of times they smoked MJ, the amount of MJ used (in grams) and the mode of use each time (i.e., joint, blunt, bong, etc.). Lifetime use was also assessed using the SCID-P and guided substance use interviews.

Statistical Analyses

In order to ensure that groups were well-matched, one-way analyses of variance (ANOVAs) with Scheffé all pairwise post hoc comparisons (two-tailed) were used to compare the four groups on all continuous demographic variables: age, IQ, ASI alcohol use (days/month), and FTND. As analyses identified age as a potential confounding variable, analyses of covariance (ANCOVAs) controlling for age were performed for all comparisons in which age was significantly different between the groups. In addition, chi-squared analyses were used to compare the sex frequencies between the four groups and to compare medication in the BP and MJBP groups. One-way ANOVAs (two-tailed) were conducted to compare age of BP onset in the BP and MJ BP groups, as well as MJ use variables in the MJ and MJBP groups, including age of MJ onset (defined as first *regular* use: a measurable, consistent pattern of use that occurred at least monthly); frequency of MJ use (average number of smoking episodes per week); magnitude of MJ use (average amount, in grams, used each week); duration of use (number of years since onset of regular MJ use); and urinary THC concentration (ng/mL).

EMA analyses

Average mood scores over the entire four-week EMA data collection period were calculated for all clinical rating scales for each individual. Additionally, for MJ-smoking participants (MJ & MJBP groups), clinical rating scales were coded to indicate whether each rating was collected before (pre) or after (post) MJ use and, with this information, “average pre-MJ use” and “average post-MJ use” ratings scales were calculated for each individual. As previously mentioned, a four-hour threshold was utilized, such that all scales completed within four hours of MJ use were coded as post-MJ use ratings. Ratings completed before MJ use each day, as well as those completed in excess of four hours after MJ use were labeled as pre-MJ use ratings. In an effort to obtain at least one daily baseline rating per day, participants were asked to complete their first set of clinical rating scales prior to smoking MJ. Obtaining overall mood rating averages for each individual, as well as pre- and post-MJ use ratings in the MJ and MJBP participants, provided the opportunity to conduct several levels of analyses in order to assess the unique effects of MJ and BPD on mood, as described below.

One-way ANCOVAs controlling for age were used to analyze differences between the four groups. In order to reduce the number of unnecessary pairwise comparisons, one-tailed Dunnett *t* post hoc comparisons were employed to compare each group to the HC control group. More specifically, to assess the effects of MJ use on both mood and cognition, the HC and MJ groups were directly compared. Similarly, the effect of BPD was examined by comparing the HC group to the “pure” BP group. The additive effect of MJ use and BPD was assessed by comparing the HC group to the MJBP group, and additional one-way ANCOVAs (one-tailed) were also conducted in order to compare the BP group to the MJBP group. These analyses were

performed on the overall average mood ratings from the EMA data and, to determine whether significant between-groups differences in overall mood were affected by MJ use, ANCOVAs were repeated using the pre-MJ use average mood ratings, and again using the post-MJ use average mood ratings from the MJ-using groups (MJ and MJBP). In addition, in order to investigate the acute effects of MJ on mood *within* both the MJ and MJBP groups, pre-MJ use average mood scores were compared to post-MJ use average mood scores using paired *t* tests (one-tailed) in each of these two groups separately.

EMA compliance analyses and controlling for missing data. Compliance checks were completed during weekly visits and involved saving the EMA data from the PDA to ensure that subjects were completing the majority of their scales. Subjects were informed of their level of compliance at each check-in visit and were encouraged to complete as many scales as possible during the following week. Overall compliance percentages were calculated for each subject. One-way ANOVAs with two-tailed Scheffé all pairwise post hoc comparisons were used to assess compliance percentage differences between the four groups. Additionally, two-tailed Pearson correlations between compliance percentage and EMA average rating scales were used to ensure that missing data did not significantly impact or skew the study findings.

Neuropsychological assessment statistical analyses. To examine the effect of BPD on cognition, regardless of MJ use status, one-way two-group ANCOVAs (2-tailed) controlling for age were performed to compare HC participants to participants with BPD (BP and MJBP groups combined). One-way, three-group ANCOVAs with Scheffé all-pairwise post hoc comparisons (2-tailed) were also conducted to compare the HC, BP, and MJBP participants. These three-group analyses assessed the impact of BPD on cognition *exclusive* of MJ use (HC vs BP), and addressed any potential additive effects of MJ use in BP patients (HC vs MJBP and BP vs MJBP).

Results

Demographics

Demographics are reported in [Table 1](#). ANOVAs of demographic variables between the four groups revealed that the groups were well matched for IQ and alcohol use (days/month). Between-group differences were noted for age ($F(3,70) = 5.819, p = .001$); Scheffé post hoc comparisons indicated that the BP subjects were significantly older than both HC ($p = .029$), and MJ ($p = .002$) participants. Accordingly, age differences were controlled for by utilizing ANCOVAs in all analyses of mood and cognitive performance. Chi-squared analyses indicated that the groups were not well matched for sex ($X^2(3, N = 74) = 11.628, p = .009$) with the MJBP group having a significantly lower percentage of females than the HC ($X^2(1, N = 33) = 8.972, p = .003$) and BP groups ($X^2(1, N = 30) = 6.914, p = .009$). Average scores on the FTND reflected very low nicotine use across the groups. However, between-group differences were noted ($F(3,70) = 6.335, p = .001$); the MJBP group reported significantly more nicotine use relative to the HC ($p = .002$), MJ ($p = .019$) and BP ($p = .004$) groups. All of the other groups reported similar FTND scores to one another, and given such low use indicated by the total scores, even for the MJBP group ($M = 1.92, SD = 3.00$), it is unlikely that nicotine use was a confound for subsequent analyses.

Analyses of medication use revealed that the BP and MJBP groups reported similar medication regimens ([Table 2](#)). No significant differences were noted for the frequency of use of different classes of medications: mood stabilizers, antidepressants, antipsychotics, and benzodiazepines. There were also no significant differences between the BP and MJBP groups for the number of medicated vs unmedicated patients within each group. In addition, the BP and MJBP groups were well-matched for age of BPD onset. With regard to MJ use characteristics,

Table 1. ANOVAs for 4-group comparison of demographic data (2-tailed).

Variable	HC	MJ	BP	MJBP	ANOVA		Scheffé All Pairwise Post Hoc Comparisons					
					F	p (η^2)	HC v MJ	HC v BP	HC v MJBP	MJ v BP	MJ v MJBP	BP v MJBP
n Sex	21 (8M, 13F)	23 (16M, 7F)	18 (8M,10F)	12 (11M,1F)	-	-	-	-	-	-	-	-
Age	23.38 (4.20)	21.96 (5.07)	28.56 (6.70)	23.75 (4.45)	5.819	.001 (.200)	NS	.029	NS	.002	NS	NS
IQ	124.65 (8.15)	119.61 (14.35)	119.17 (9.92)	115.00 (9.62)	1.948	.130 (.079)	NS	NS	NS	NS	NS	NS
Alcohol Use (days/month)	5.24 (5.44)	7.18 (6.05)	3.94 (5.71)	5.17 (4.71)	1.133	.342 (.048)	NS	NS	NS	NS	NS	NS
BPD Age of Onset	-	-	18.06 (4.53)	15.21 (3.17)	3.556	.070 (.113)	-	-	-	-	-	-
MJ Age of Onset	-	16.35 (2.31)	-	16.92 (2.61)	0.438	.513 (.013)	-	-	-	-	-	-
MJ Smokes/Week	-	15.99 (7.39)	-	15.55 (13.63)	0.015	.903 (<.001)	-	-	-	-	-	-
MJ Grams/Week	-	7.21 (5.55)	-	5.19 (2.76)	1.289	.265 (.039)	-	-	-	-	-	-
MJ Duration of Use (yrs)	-	5.61 (3.99)	-	6.83 (2.76)	0.901	.349 (.027)	-	-	-	-	-	-
Urinary THC (ng/mL)	-	617.53 (873.71)	-	443.13 (528.43)	0.370	.547 (.011)	-	-	-	-	-	-

doi:10.1371/journal.pone.0157060.t001

the MJ and MJBP groups were also well-matched for age of MJ onset (Table 1), as well as current levels of MJ use. In fact, no significant differences emerged between groups for frequency (smokes/week) and magnitude of MJ use (grams/week), duration of MJ use (years since onset of regular use), or urinary THC levels (ng/mL).

EMA Results

EMA compliance results and controlling for missing data. Across all groups, high levels of compliance were noted for rating scale completion, with the average overall number of completed rating scales at 88% of all possible rating opportunities. Within the HC group, EMA rating compliance indicated that they completed 94% of scales, while the BP completed 90%, and the MJ and MJBP groups each completed 84% of scales. Notably, the MJ and MJBP groups both were required to complete more rating scales than the non-smoking groups, as they rated their mood three times daily *in addition* to completing ratings after MJ use. Therefore, it is not

Table 2. Chi Squared Analyses of Medication Use in the BP and MJBP Groups.

Variable	BP	MJBP	Chi Squared	
			χ^2	p
Mood Stabilizers	72.22%	75.00%	0.028	NS
Antidepressants	27.78%	16.67%	0.497	NS
Antipsychotics	55.56%	58.33%	0.023	NS
Benzodiazepines	16.67%	8.33%	0.433	NS
Unmedicated	16.67%	8.33%	0.433	NS

(df = 1, n = 30)

doi:10.1371/journal.pone.0157060.t002

surprising that ANOVA results indicated that despite very high levels of compliance across all groups, some differences in compliance levels were evident ($F(3,57) = 3.238, p = .029$). Two-tailed Scheffé all pairwise post hoc comparisons revealed that these differences were driven by a trend in which the MJ group exhibited lower percentages for completion of EMA ratings ($M = 83.71, SD = 9.81$) than the HC group ($M = 93.78, SD = 5.91, p = .055$). Compliance percentages for the BP ($M = 90.08, SD = 9.90$) and MJBP groups ($M = 84.20, SD = 19.29$) were not significantly different from the other groups. However, due to the significant between-group differences, EMA analyses were re-run with compliance percentage as a covariate, and results remained unchanged. Further, in order to determine the nature of missing EMA data, correlation analyses were also conducted to assess the association between compliance percentage and EMA clinical ratings. Compliance percentage did not significantly correlate with any clinical rating scale ($r(59) \leq .203, p \geq .12$), suggesting that ratings were missing at random, and therefore missing EMA data did not unduly influence clinical mood ratings results.

Between-group analyses. Overall average mood ratings from across the 4-week data collection period are presented in [Table 3](#). As expected, compared to the HC group, BP and MJBP participants reported higher levels of anger, confusion, tension, fatigue, depression, and total mood disturbance (TMD) as measured by the POMS, as well as increased anxiety (HAM-A), depression (MADRS), and mania (YMRS). Among patients, those in the BP group reported similar overall mood to MJBP participants, with no significant differences observed on any rating scale, with the exception of higher MADRS scores in the MJBP group. Despite this difference, depression ratings on the POMS were similar between groups, and actually were slightly (albeit not significantly) lower in the MJBP group relative to the BP group. With regard to the MJ group, no significant differences were noted between MJ smokers and HCs for average mood ratings.

Analyses of average *pre*-MJ use mood data in the MJ and MJBP group compared to overall average mood in the HC and BP group are presented in [Table 4](#) (top portion of table); analyses of average *post*-MJ mood data in the MJ and MJBP group compared to overall average mood in the HC and BP group are presented in [Table 4](#) (bottom half of table). *Prior to* smoking MJ, the MJBP participants reported higher levels of anger, confusion, tension, depression, and TMD on the POMS, as well as greater anxiety, depression, and mania as measured by the HAM-A, MADRS, and YMRS, relative to the average mood ratings of the HC participants. *After* smoking MJ, while some significant differences remained between the MJBP and HC groups, the MJBP group no longer endorsed significantly higher anger, tension, or TMD on the POMS relative to the HCs. Notably, the MJ participants did not report significantly different mood ratings compared to the HC participants either *pre*- or *post*-MJ use.

Two-group ANCOVAs directly comparing the BPD patient groups (BP vs MJBP; [Table 4](#)) revealed that *prior to MJ* use, MJBP participants exhibited higher depression (MADRS) scores and a trend for higher mania (YMRS) ratings relative to the BP group. Interestingly, *after smoking MJ*, the MJBP group reported decreased levels of depression and mania; MADRS scores fell to a level no longer significantly different from ratings in the BP group, and the trend for higher mania ratings on the YMRS was no longer observed in MJBP participants relative to BP participants. In addition, the MJBP group reported a trend for lower levels of tension on the POMS after MJ use compared to BP patients. Together, these decreases in clinical symptoms led to far lower TMD scores in the MJBP group *after MJ* use, relative to the BP group's average TMD score (MJBP: 11.15 vs BP: 22.53); however, this difference was not statistically significant.

Within-group analyses. Paired *t* tests investigating within-group mood changes *pre*- and *post MJ* use suggest that *after* smoking MJ, the MJ smokers experienced slightly worse mood overall. As a group, they reported significantly increased confusion and fatigue, and decreased

Table 3. ANCOVAs (controlling for age differences) of the 4-group (HC, MJ, BP, MJBP with Dunnett *t* post hoc comparisons) and 2-group (BP v MJBP) comparisons of overall 4-week average mood EMA ratings (1-tailed).

Variable	HC	MJ	BP	MJBP	4-group ANCOVA		4-group Dunnett <i>t</i> Post Hoc Comparisons			2-group BP v MJBP ANCOVA	
					<i>F</i>	<i>p</i> (η^2)	HC v MJ	HC v BP	HC v MJBP	<i>F</i>	<i>p</i> (η^2)
<i>n</i>	18	21	12	10	-	-	-	-	-	-	-
POMS											
Vigor	11.13 (3.77)	12.92 (4.73)	9.71 (3.67)	9.39 (3.23)	2.039	.060 (.098)	NS	NS	NS	0.357	.279 (.018)
Anger	0.86 (0.76)	1.31 (1.71)	4.24 (3.41)	4.14 (2.59)	7.616	<.001 (.290)	NS	<.001	<.001	0.355	.279 (.018)
Confusion	3.48 (1.44)	3.51 (1.81)	7.06 (3.39)	5.76 (2.69)	5.951	<.001 (.242)	NS	<.001	.019	0.022	.442 (.001)
Tension	3.27 (1.30)	2.71 (1.61)	6.92 (3.37)	6.48 (3.94)	7.851	<.001 (.296)	NS	<.001	.003	0.187	.335 (.010)
Fatigue	3.07 (1.86)	2.00 (1.65)	7.06 (3.48)	5.08 (2.99)	8.843	<.001 (.321)	NS	<.001	.050	0.219	.323 (.011)
Depression	1.31 (1.37)	1.06 (2.07)	6.95 (7.04)	6.61 (5.17)	6.462	.001 (.257)	NS	<.001	.002	0.570	.230 (.029)
TMD	0.86 (7.58)	-2.33 (9.52)	22.53 (21.17)	18.68 (17.41)	8.686	<.001 (.318)	NS	<.001	.002	0.196	.332 (.010)
HAMA	0.68 (0.65)	0.86 (1.23)	4.43 (3.44)	4.82 (3.92)	9.904	<.001 (.347)	NS	<.001	<.001	0.771	.120 (.039)
MADRS	1.52 (1.37)	1.57 (2.00)	7.21 (5.43)	10.60 (7.01)	14.832	<.001 (.443)	NS	<.001	<.001	3.183	.045 (.143)
YMRS	1.56 (0.84)	1.50 (1.42)	3.99 (3.23)	5.64 (2.83)	8.193	<.001 (.305)	NS	.008	<.001	1.693	.105 (.082)

POMS = Profile of Mood States, TMD = Total Mood Disturbance, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

doi:10.1371/journal.pone.0157060.t003

vigor on the POMS, resulting in higher TMD scores relative to pre-smoking levels. It is of note, however, that their average TMD scores still fell below zero, reflecting very low levels of mood-related symptomatology overall. MJ smokers also reported higher levels of anxiety (HAM-A) after MJ use (Fig 1A). In contrast, the MJBP participants reported positive changes in mood after MJ use. Paired *t* tests comparing pre- and post-MJ use mood ratings within the MJBP group indicated significantly decreased ratings of anger, tension, depression, and TMD scores on the POMS as well as lower levels of depression on the MADRS. In addition, MJBP participants reported increased vigor on the POMS after MJ use (Fig 1B).

Neuropsychological Assessment

HC vs All BP: Effects of BPD on cognition (regardless of MJ use status). When all BPD patients (BP and MJBP combined) were compared to the HC group, they generally demonstrated poorer performance on tasks of executive function. Specifically, as noted in Table 5, 2-way ANCOVAs revealed that patients with BPD achieved fewer categories, made more perseveration errors and had more losses of set on the WCST. Patients with BPD had significantly longer completion times and made more errors on the Stroop during the Color Naming and Word Reading condition. They also demonstrated slightly slower completion times on the Stroop Interference condition relative to the HCs, although this did not reach statistical significance. Similarly, BPD patients also performed Trails B significantly more slowly and exhibited

Table 4. Pre- vs Post-MJ Use Mood in MJ and MJBIP Participants: ANCOVAs (controlling for age differences) of the 4-group (HC, MJ, BP, MJBIP with Dunnett *t* post hoc comparisons) and 2-group (BP v MJBIP) comparisons of overall 4-week average mood in the HC and BP participants to average pre- and post-MJ use mood in the MJ and MJBIP participants (1-tailed).

Variable	HC (avg)	MJ (pre)	BP (avg)	MJBIP (pre)	4-group ANCOVA		4-group Dunnett <i>t</i> Post Hoc Comparisons			2-group ANCOVA BP v MJBIP	
					<i>F</i>	<i>p</i> (η^2)	HC v MJ	HC v BP	HC v MJBIP	<i>F</i>	<i>p</i> (η^2)
<i>n</i>	18	21	12	10	-	-	-	-	-	-	-
PRE MJ USE											
POMS											
Vigor	11.13 (3.77)	13.67 (5.50)	9.71 (3.67)	9.26 (2.96)	2.792	.025 (.130)	NS	NS	NS	0.672	.211 (.034)
Anger	0.86 (0.76)	1.29 (1.84)	4.24 (3.41)	4.52 (3.14)	7.604	<.001 (.289)	NS	<.001	<.001	0.728	.202 (.037)
Confusion	3.48 (1.44)	3.00 (1.64)	7.06 (3.39)	6.43 (2.96)	8.455	<.001 (.312)	NS	<.001	.003	0.133	.360 (.007)
Tension	3.27 (1.30)	2.69 (2.12)	6.92 (3.37)	7.53 (4.41)	8.933	<.001 (.324)	NS	.001	<.001	1.166	.147 (.058)
Fatigue	3.07 (1.86)	1.68 (1.70)	7.06 (3.48)	4.77 (3.05)	9.290	<.001 (.332)	NS	<.001	NS	0.464	.252 (.024)
Depression	1.31 (1.37)	0.71 (1.11)	6.95 (7.04)	7.40 (6.06)	8.086	<.001 (.302)	NS	<.001	<.001	0.904	.177 (.045)
TMD	0.86 (7.58)	-4.30 (8.86)	22.53 (21.17)	21.39 (19.68)	10.608	<.001 (.362)	NS	<.001	<.001	0.590	.226 (.030)
HAMA	0.68 (0.65)	0.61 (1.13)	4.43 (3.44)	5.06 (4.15)	10.997	<.001 (.371)	NS	<.001	<.001	0.980	.168 (.049)
MADRS	1.52 (1.37)	1.41 (1.63)	7.21 (5.43)	11.91 (7.53)	18.538	<.001 (.498)	NS	<.001	<.001	5.317	.017 (.219)
YMRS	1.56 (0.84)	1.90 (2.44)	3.99 (3.23)	6.10 (3.89)	7.762	<.001 (.294)	NS	.020	<.001	2.084	.083 (.009)
POST MJ USE											
POMS											
Vigor	11.13 (3.77)	12.02 (4.65)	9.71 (3.67)	10.78 (3.52)	0.656	.292 (.034)	NS	NS	NS	0.095	.381 (.005)
Anger	0.86 (0.76)	1.43 (1.78)	4.24 (3.41)	2.35 (2.54)	4.840	.003 (.206)	NS	<.001	NS	0.953	.171 (.048)
Confusion	3.48 (1.44)	3.63 (1.68)	7.06 (3.39)	5.85 (3.11)	5.771	.001 (.236)	NS	<.001	.017	0.021	.443 (.001)
Tension	3.27 (1.30)	2.54 (1.66)	6.92 (3.37)	4.15 (2.62)	7.707	<.001 (.292)	NS	<.001	NS	2.473	.066 (.115)
Fatigue	3.07 (1.86)	2.77 (2.72)	7.06 (3.48)	4.88 (3.24)	5.186	.002 (.217)	NS	<.001	NS	0.430	.260 (.022)
Depression	1.31 (1.37)	0.77 (1.23)	6.95 (7.04)	4.69 (3.64)	6.073	.001 (.245)	NS	<.001	.026	0.030	.433 (.002)
TMD	0.86 (7.58)	-0.87 (10.32)	22.53 (21.17)	11.15 (13.69)	6.626	.001 (.262)	NS	<.001	NS	0.511	.242 (.026)
HAMA	0.68 (0.65)	0.82 (1.08)	4.43 (3.44)	4.23 (4.12)	8.315	<.001 (.308)	NS	<.001	<.001	0.065	.401 (.003)
MADRS	1.52 (1.37)	1.46 (1.71)	7.21 (5.43)	9.35 (6.89)	12.229	<.001 (.397)	NS	<.001	<.001	1.341	.131 (.066)
YMRS	1.56 (0.84)	2.30 (1.96)	3.99 (3.23)	5.61 (3.81)	6.856	.001 (.269)	NS	.013	<.001	1.091	.155 (.054)

POMS = Profile of Mood States, TMD = Total Mood Disturbance, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

doi:10.1371/journal.pone.0157060.t004

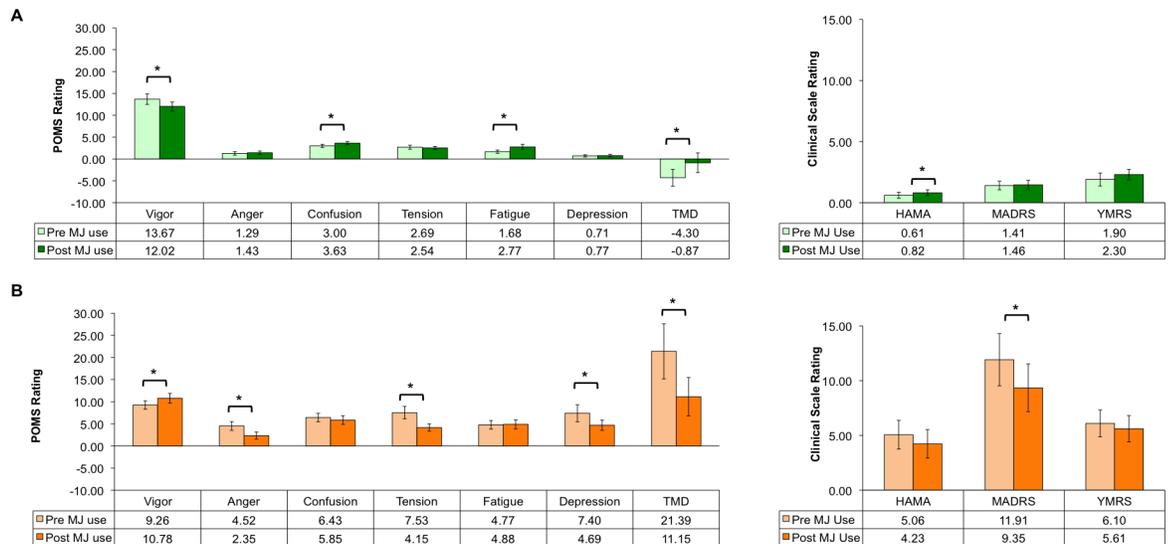


Fig 1. Paired t-Test EMA Analyses of Clinical State Pre- versus Post-MJ Use. EMA analyses of clinical state (POMS, HAMA, MADRS, YRMS) changes pre- versus post-MJ use in the (A) MJ group and (B) MJBP group revealed a slight worsening of symptoms in the MJ group after smoking MJ but a significant mood improvement in the MJBP group after smoking MJ, * $t(\geq 9) \geq 1.942, p \leq .042$, 1-tailed. POMS = Profile of Mood States, TMD = Total Mood Disturbance, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale

doi:10.1371/journal.pone.0157060.g001

a trend for more errors on Trails A relative to HCs. BPD patients achieved lower total scores across the three trials of the COWAT in which they had to generate words starting with a given letter (F, A, S); during the semantic category trial (animals) a trend was also observed for fewer words generated among BPD patients. In addition, BPD patients recalled fewer digits on Digit Span overall, including recollection of digits in forward order (Forward) and in reverse order (Backward), which led to lower Total Digit Span scores.

On the remaining measures, BPD patients also tended to demonstrate reduced performance. Despite similar scores on the copy condition of the ROCF, they exhibited slightly lower scores on the immediate recall condition, and achieved significantly lower scores on delayed recall relative to the HCs. On the CVLT, BPD patients recalled fewer words during the initial learning trial (Trial 1), as well as across all five trials (Trial 1–5 Total Correct), and after the Long Delay. They also used less semantic clustering on the CVLT across the five trials (Trial 1–5 Total Semantic Clusters). No significant differences in performance were apparent on the HVOT.

HC vs BP: Effects of BPD on cognition (exclusive of MJ use). Post hoc analyses from a three-way ANCOVA comparing HC, BP and MJBP patients revealed that, relative to HCs, the non-MJ smoking BP participants (BP group only) demonstrated similar deficits when examined separate from the MJBP group as when grouped with MJBP participants (see Table 5). The BP group exhibited poorer performance across the majority of assessment measures. Non-MJ smoking BP patients achieved significantly fewer categories on the WCST; they also made more perseverative errors, and had more losses of set, although this did not reach the threshold for significance. Participants in the BP group also made more errors on the Stroop Color Naming and Word Reading subtests. They took significantly longer to complete Trails B, and exhibited a trend for more Trails B errors. Further, they recalled slightly fewer digits across on Digit Span Backwards, which contributed to significantly lower scores on the Total Digit Span scores among BPD patients relative to HCs. On the CVLT, the BP group recalled fewer words than

Table 5. Neuropsychology Data and Between-Groups Comparisons: ANCOVAs (controlling for age) of the 2-group (HC v All BP) and 3-group (HC, BP, and MJBP) comparisons (2-tailed).

Variable	HC	All BP	BP	MJBP	2-group ANCOVA HC v All BP		3-group ANCOVA HC v BP v MJBP		Scheffé All Pairwise Post Hoc Comparisons		
					F	p (η^2)	F	p (η^2)	HC vs BP	HC vs MJBP	BP vs MJBP
n	21	30	18	12	-	-	-	-	-	-	-
WCST											
Total Categories	9.30 (0.98)	8.21 (1.26)	8.29 (1.31)	8.08 (1.24)	9.598	.003 (.173)	4.858	.012 (.178)	.041	.023	NS
Total Perseverations	6.40 (4.44)	10.72 (7.30)	10.00 (7.16)	11.75 (7.69)	5.718	.021 (.111)	2.996	.060 (.118)	NS	.080	NS
Total Losses of Set	0.15 (0.37)	0.59 (0.87)	0.59 (0.87)	0.58 (0.90)	4.694	.035 (.093)	2.318	.110 (.093)	NS	NS	NS
Stroop											
Color Naming Time (sec)	49.60 (7.47)	54.33 (9.01)	52.17 (7.29)	57.58 (10.61)	4.148	.047 (.081)	3.444	.040 (.130)	NS	.038	NS
Color Naming Errors	0.55 (1.00)	1.37 (1.33)	1.67 (1.50)	0.92 (0.90)	5.495	.023 (.105)	4.811	.013 (.173)	.021	NS	NS
Word Reading Time (sec)	38.95 (4.39)	42.10 (5.82)	41.56 (5.95)	42.92 (5.78)	6.539	.014 (.122)	3.201	.050 (.122)	NS	NS	NS
Word Reading Errors	0.35 (0.59)	0.93 (1.05)	1.11 (1.08)	0.67 (0.98)	5.041	.029 (.097)	3.781	.030 (.141)	.039	NS	NS
Interference Time (sec)	85.75 (15.60)	91.63 (15.94)	89.56 (16.13)	94.75 (15.82)	2.763	.103 (.056)	1.435	.248 (.059)	NS	NS	NS
Interference Errors	2.10 (1.94)	2.03 (2.11)	2.33 (2.35)	1.58 (1.68)	0.046	.831 (.001)	1.172	.319 (.048)	NS	NS	NS
Trail Making Test											
A Time (sec)	20.85 (6.29)	24.07 (8.55)	23.33 (6.45)	25.17 (11.24)	1.919	.173 (.039)	1.160	.322 (.048)	NS	NS	NS
A Errors	0.10 (0.31)	0.30 (0.53)	0.39 (0.61)	0.17 (0.39)	3.351	.074 (.067)	3.655	.034 (.137)	NS	NS	NS
B Time (sec)	38.85 (11.21)	54.23 (19.86)	55.50 (21.75)	52.33 (17.38)	7.670	.008 (.140)	3.770	.030 (.141)	.016	NS	NS
B Errors	0.15 (0.49)	0.40 (0.62)	0.56 (0.70)	0.17 (0.39)	0.992	.663 (.004)	1.356	.268 (.056)	.093	NS	NS
COWAT											
Total (FAS)	47.65 (8.78)	39.14 (11.58)	38.25 (11.69)	40.20 (11.98)	7.318	.010 (.158)	3.835	.030 (.168)	.060	NS	NS
Semantic Category	26.45 (6.42)	22.59 (4.82)	22.25 (5.67)	23.00 (3.80)	3.146	.084 (.075)	1.552	.225 (.076)	NS	NS	NS
Digit Span											
Forward	9.80 (2.09)	8.50 (2.35)	8.24 (2.54)	8.91 (2.07)	4.262	.045 (.087)	2.681	.080 (.109)	NS	NS	NS
Backward	8.85 (2.50)	7.18 (1.87)	7.18 (2.24)	7.18 (1.17)	9.792	.003 (.179)	5.063	.010 (.187)	.077	NS	NS
Total	18.65 (4.06)	15.68 (3.58)	15.41 (4.06)	16.09 (2.81)	8.993	.004 (.167)	5.009	.001 (.185)	.046	NS	NS
ROCF											
Copy	33.00 (2.92)	30.93 (3.71)	31.04 (4.45)	30.80 (2.79)	2.491	.123 (.063)	1.325	.278 (.069)	NS	NS	NS
Immediate	22.69 (7.55)	16.93 (7.30)	16.83 (8.26)	17.05 (6.41)	3.019	.091 (.075)	1.778	.184 (.090)	NS	NS	NS

(Continued)

Table 5. (Continued)

Variable	HC	All BP	BP	MJB	2-group ANCOVA HC v All BP		3-group ANCOVA HC v BP v MJB		Scheffé All Pairwise Post Hoc Comparisons		
					F	p (η^2)	F	p (η^2)	HC vs BP	HC vs MJB	BP vs MJB
<i>n</i>	21	30	18	12	-	-	-	-	-	-	-
Delay	22.81 (6.82)	16.68 (6.58)	16.63 (6.91)	16.75 (6.54)	4.957	.031 (.118)	2.660	.084 (.129)	.062	.091	NS
CVLT											
Trial 1 Correct	8.25 (1.89)	6.46 (1.91)	6.88 (1.83)	5.82 (1.94)	8.997	.004 (.167)	6.005	.005 (.214)	NS	.005	NS
Total Correct	61.10 (8.14)	51.18 (10.53)	53.35 (11.75)	47.82 (7.61)	10.182	.003 (.185)	7.192	.002 (.246)	.057	.002	NS
Total Perseverations	4.75 (5.44)	5.57 (4.76)	5.29 (4.78)	6.00 (4.94)	0.331	.568 (.007)	0.212	.810 (.010)	NS	NS	NS
Total Intrusions	1.60 (2.14)	1.11 (2.74)	0.53 (1.23)	2.00 (4.05)	0.669	.418 (.015)	2.130	.131 (.088)	NS	NS	NS
Total Semantic Clusters	27.10 (11.09)	18.57 (13.01)	21.47 (14.82)	14.09 (8.34)	4.393	.042 (.089)	4.262	.020 (.162)	NS	.023	NS
Long Delay Correct	13.90 (1.68)	10.64 (3.68)	10.65 (4.14)	10.64 (3.04)	10.328	.002 (.187)	5.239	.009 (.192)	.009	.024	NS
HVOT											
Total	26.56 (1.76)	26.41 (1.88)	25.71 (2.03)	27.25 (1.34)	0.016	.901 ($<.001$)	2.063	.142 (.103)	NS	NS	NS

WCST = Wisconsin Card Sorting Test, ROCF = Rey-Osterrieth Complex Figure, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, HVOT = Hooper Visual Organization Test.

doi:10.1371/journal.pone.0157060.t005

HCs on the CVLT across all five trials and after a delay. On the COWAT and ROCF, although results were not significant, the BP group demonstrated several trends for worse performance, as noted in Table 5. No deficits were noted the HVOT between HCs and the BP group.

HC vs MJ: Effects of MJ use on cognition (exclusive of BPD diagnosis). Similar to our previous report of MJ smokers [43], two-way ANCOVAs directly comparing MJ smokers to HCs demonstrated that pure MJ smokers exhibited impairment on a number of tasks relative to HCs, including the WCST, Trail Making Test, COWAT, and CVLT (See Table 6). Specifically, as noted in the BPD patients, MJ smokers demonstrated poorer executive functioning relative to controls. They achieved fewer categories and made more perseverative errors on the WCST, and took longer to complete Trails B of the Trail Making Test. MJ smokers generated fewer words than HCs on the COWAT when asked to provide words in a given semantic category. On the CVLT, although MJ smokers recalled a similar number of correct words, they had more Intrusions (incorrect responses) and utilized less semantic clustering across trials (Total Semantic Clusters). HC and MJ participants did not differ significantly with regard to their performance of the Stroop Color Word Test, Digit Span, ROCF, or HVOT.

HC vs MJB and BP vs MJB: Potential additive effects of BPD and MJ use. Post hoc analyses from three-way ANCOVAs (HC vs BP vs MJB) designed to detect potential additive effects of BPD and MJ use revealed that MJB patients demonstrated some areas of poorer cognitive performance relative to HCs (see Table 5, HC vs MJB). They achieved fewer categories on the WCST and their performance suggests a trend for making more perseverative errors on this task. On the Stroop, significantly slower times were noted relative to HCs on the Color Naming subtest, while on the CVLT, MJB participants recalled significantly fewer words

Table 6. Neuropsychology Data and Between-Groups Comparisons: ANCOVAs (controlling for age differences) of the 2-group (HC v MJ) comparisons (1-tailed).

Variable	HC	MJ	2-group ANCOVA	
			F	p (η^2)
n	20	23		
WCST				
Total Categories	9.30 (0.98)	8.73 (1.55)	6.746	.007 (.147)
Total Perseverations	6.40 (4.44)	10.50 (8.55)	12.680	.001 (.245)
Total Losses of Set	0.15 (0.37)	0.36 (0.73)	2.502	.061 (.060)
Stroop Color Word Test				
Color Naming Time (sec)	49.60 (7.47)	52.26 (8.43)	1.449	.118 (.035)
Color Naming Errors	0.55 (1.00)	1.09 (1.12)	2.281	.070 (.054)
Word Reading Time (sec)	38.95 (4.39)	39.65 (4.51)	0.256	.308 (.006)
Word Reading Errors	0.35 (0.59)	0.43 (0.59)	0.248	.311 (.006)
Interference Time (sec)	85.75 (15.60)	86.96 (14.50)	0.273	.302 (.007)
Interference Errors	2.10 (1.94)	2.65 (2.25)	0.802	.188 (.020)
Trail Making Test				
A Time (sec)	20.85 (6.29)	20.95 (4.53)	0.122	.365 (.003)
A Errors	0.10 (0.31)	0.18 (0.39)	0.231	.317 (.006)
B Time (sec)	38.85 (11.21)	50.50 (22.65)	4.784	.018 (.109)
B Errors	0.15 (0.49)	0.32 (0.48)	0.863	.180 (.022)
COWAT				
Total (FAS)	47.65 (8.78)	48.45 (11.43)	0.035	.426 (.001)
Semantic Category	26.45 (6.42)	21.86 (5.59)	7.134	.006 (.155)
Digit Span				
Forward	9.80 (2.09)	9.78 (2.39)	0.010	.462 (<.001)
Backward	8.85 (2.50)	8.70 (2.24)	0.113	.370 (.003)
Total	18.65 (4.06)	18.48 (3.82)	0.021	.443 (.001)
ROCF				
Copy	33.00 (2.92)	32.72 (3.33)	0.206	.327 (.005)
Immediate	22.69 (7.55)	22.42 (7.01)	0.078	.391 (.002)
Delayed	22.81 (6.82)	22.07 (6.65)	0.239	.314 (.006)
CVLT				
Trial 1 Correct	8.25 (1.89)	7.39 (2.41)	2.381	.065 (.056)
Total Correct	61.10 (8.14)	57.52 (8.95)	2.717	.054 (.064)
Total Perseverations	4.75 (5.44)	5.57 (5.47)	0.155	.348 (.004)
Total Intrusions	1.60 (2.14)	0.57 (0.90)	3.637	.032 (.083)
Total Semantic Clusters	27.10 (11.09)	21.61 (8.52)	4.347	.022 (.098)
Long Delay Correct	13.90 (1.68)	13.09 (3.13)	2.596	.058 (.061)
HVOT	26.56 (1.76)	26.80 (2.18)	0.133	.359 (.004)

WCST = Wisconsin Card Sorting Test, ROCF = Rey Osterrieth Complex Figure, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, HVOT = Hooper Visual Organization Test

doi:10.1371/journal.pone.0157060.t006

during Trial 1, throughout all five learning trials, and after a 20-minute delay. MJBP participants also had fewer semantic clusters on the CVLT. On the ROCF, like the pure BP group, MJBP participants exhibited a trend for lower scores on the Delayed Recall; however, they did not exhibit impairment on the remaining conditions of the task, nor did they demonstrate impaired performance on the Trail making Test, Digit Span, or HVOT relative to HCs.

Although BPD patients and MJ smokers each demonstrated impairment on several measures of cognitive performance relative to HCs, *no differences emerged* when directly comparing the BP and MJBP groups (see [Table 5](#), BP vs MJBP). In fact, Scheffé all pairwise post hoc comparisons revealed no significant between-group differences for BP vs MJBP participants for any task: WCST, Stroop, Trail Making Test, COWAT, CVLT, ROCF, Digit Span, or HVOT.

Discussion

The current investigation, to our knowledge, marks the first study to examine the effects of MJ on both mood and neuropsychological performance in BPD patients. As the nation explores indications for medical MJ (MMJ), it is imperative to determine how MJ use might affect clinical symptoms in those diagnosed with mood disorders, such as BPD. In addition, given the fact that cognitive decrements are well-documented in both MJ smokers [[43](#), [62–64](#)] and those with BPD [[39](#), [65](#)], it is critical to examine whether these impairments may be exacerbated or possibly ameliorated by the combination of a BPD diagnosis and regular MJ use. Through the utilization of proper control groups (achieved by including four discrete groups: healthy controls, MJ smokers with no Axis I pathology, non-MJ smoking BP patients, and MJ-smoking BP patients), the current study was able to begin to clarify both the individual effects and potential for additive effects of MJ use and BPD on mood and cognition.

As hypothesized, our findings suggest that after smoking MJ, BPD patients experienced improvement in several aspects of clinical state secondary to MJ use. In fact, direct analyses of the MJ-smoking BPD patients (MJBP) *before* and *after* MJ use revealed notable symptom alleviation within four hours of smoking. After smoking MJ, the MJBP group reported significantly lower scores of anger, tension, depression (POMS and MADRS), as well as higher levels of vigor, which led to a marked decrease in TMD scores (22.39 to 11.15), a composite measure of overall mood on the POMS. Further, prior to smoking MJ, the MJBP participants reported slightly worse levels of symptomatology relative to the pure BP group, with higher levels of depressive and manic symptoms. In contrast, after MJ use, the MJBP group demonstrated considerably *lower* levels of tension and lower TMD scores relative to the BP group. In addition, although depression (MADRS) and mania scores were still slightly higher in the MJBP group after MJ use relative to the BP group, scores dropped to levels that were no longer significant or approaching significance between the two groups, highlighting positive changes in mood-related symptoms. In addition, average mood ratings across the course of the study showed that overall mood was comparable between MJBP and BP subjects. Although MADRS scores were generally elevated in MJBP patients, POMS scores for depression were similar between groups (and were actually marginally lower within MJBP participants). As the MADRS reflects specific depressive symptoms, as compared to the POMS which measures self-perceived mood, results may indicate that while certain depressive symptoms were more evident in MJBP participants relative to BP participants, a *self-perceived* mood of depression (i.e., feeling sad, lonely, blue) was not more prevalent in MJBP participants.

To some extent, these findings support recent work, which found that MJ use was correlated with increased positive affect in BPD patients [[66](#)]. However, the authors also observed a relationship between MJ use and increased manic and depressive symptoms. Although the authors of this study report both positive and negative fluctuations in clinical symptoms, they posit that bidirectional effects of MJ use, outlined by Ashton and colleagues [[22](#)], are likely impacted by a range of factors, including dose, mode of use, and personality differences. In addition, as we learn more about the differential effects of individual constituents of MJ, (i.e., THC vs cannabidiol [CBD]), it is possible that strains higher in certain constituents are at least partially

responsible for the moderation of specific dimensions of clinical symptoms. Some research suggests that CBD may be beneficial in alleviating, anxiety, psychosis, and other psychological symptoms [67–70] and may have a pharmacological profile similar to that of antipsychotic medications [69], which are often prescribed to patients with bipolar I disorder. Further, CBD has been shown to be an effective anticonvulsant treatment for those with pediatric seizure disorders [70], another class of drugs frequently prescribed for mood stabilization in patients with BPD.

Interestingly, among pure MJ smokers (those not diagnosed with BPD), beneficial effects on mood were *not* observed in the current study. MJ smokers reported decreases in vigor, as well as higher levels of confusion, fatigue and TMD after smoking, consistent with effects commonly reported in the general population after MJ use. It is of note, however, that MJ smokers continued to exhibit very low levels of mood-related symptoms even after MJ use, suggesting that while their mood did appear to worsen slightly after using MJ, these changes remained far below clinical thresholds. Overall, results may indicate that MJ use may have unique effects in BPD patients, effects which are not necessarily observed in those without Axis I pathology.

With regard to cognitive performance, MJ smokers and BPD patients performed more poorly than HCs overall. However, within the BPD patients, impairment was observed *regardless* of MJ use status; deficits were apparent when the non-smoking BP patients were analyzed as a whole group (BP and MJBP) as well as separately (BP vs MJBP). Overall, patients in both BPD groups demonstrated poorer performance on tasks of executive function. They also exhibited less efficient learning and recall strategies during a serial list-learning task, reduced verbal fluency, inferior attention and working memory, and poorer visuospatial organization. Interestingly, when the non-smoking BP group was compared to the MJBP group, no significant differences across any measure were noted. Taken together, study findings suggest that MJ use may result in at least short-term mood term stabilization for a subset of BPD patients, and further, that MJ use does not have an additive, negative impact on cognitive performance in BPD patients.

These findings provide a valuable contribution to the field, which has only begun to clarify the effects of MJ on mood and cognition in psychiatric populations. While many would posit that the individual relationships between cognitive impairment and both MJ use and BPD would collectively result in a *more severe impact* on cognitive function, some studies have actually reported a cognitive advantage in BPD patients who use MJ regularly [40–41]. In addition, a recent study of MJ-smoking patients diagnosed with schizophrenia found no evidence for an additive effect of MJ use and schizophrenia diagnosis on cognitive dysfunction [71]. In combination, these studies provide evidence that cognitive deficits associated with certain Axis I pathologies may not be worsened by MJ use. In fact, improved cognitive performance may be related to the potential anxiolytic effects of MJ. Anxiety, common in BPD patients [72], often interferes with attention and the ability to encode information, suggesting that if MJ acts as an anxiolytic in at least a subset of patients, this may result in better concentration and enhanced cognitive performance.

Despite these positive changes, one previous study also observed that patients tended to experience improved cognitive performance at the expense of a more severe clinical course [41]. While the current study did not examine long-term treatment outcomes, our preliminary findings provide evidence that BPD patients who smoke MJ may derive at least a short-term clinical benefit. MJBP participants reported improvements in mood within four hours of smoking MJ, did not have elevated average mood ratings (with the exception of the MADRS) relative to the BPD group across the four-week study, and did not experience additional cognitive deficits when compared to the non-smoking BP group. Future studies will need to be conducted in order to investigate the effect of MJ use on clinical course over longer durations of time.

Limitations

Data from the current study provide critical information about MJ use in psychiatric populations, as guidelines regarding indications for medical MJ are considered; however, these findings must be interpreted in light of several limitations. First, although this study served as a pilot investigation, it is important to acknowledge that the overall sample is moderate in size, with a modest number of patients completing EMA ratings, which may limit the generalizability of findings. For example, only participants who were well characterized as chronic, heavy MJ smokers were enrolled in the current study; participants with less frequent use (i.e., casual MJ smokers) may not experience the same effects of MJ on mood and cognition as observed in this sample of participants. Further, rather stringent enrollment criteria were employed, which excluded participants who reported comorbid diagnoses (via phone interview or through the clinical interview). In addition, participants were required to be predominantly euthymic throughout the course of the study. Although these criteria limited the effects of extraneous variables, the impact of MJ on mood and cognition may differ in those who have been diagnosed with comorbid disorders (i.e., ADHD, PTSD, polysubstance use, etc.) or who may be experiencing more acute clinical symptomatology. Finally, likely related to the geographic region from which patients were recruited (the Greater Boston area is home to many universities, hospitals, and research institutions), participants generally demonstrated higher than average IQs. This may limit generalizability to populations with average to below average cognitive abilities. It will be important for future studies to recruit larger numbers of research participants to further investigate the impact of MJ on mood and cognition in BPD, as well as to examine additional factors that were not explored in the current pilot investigation.

Additionally, although the four groups were not statistically matched for sex (more males were enrolled than females in the MJ and MJBP groups), it is likely that the sex distribution of this sample is actually representative of the larger population. In fact, national surveys of substance-using populations have revealed that males engage in the use of illicit substances, including MJ, more frequently than females [73–74].

Regarding the EMA study design, overall compliance was very high among all study groups with an overall completion rate of 88% of all possible scheduled ratings. Several measures were also put in place to encourage completion of ratings after MJ use, including comparing reported frequency of MJ use during interim visits to the frequency of EMA ratings. However, given the nature of EMA data, it is not possible to guarantee that all participants completed mood ratings immediately after MJ use. In an attempt to address this issue, all participants were asked to adjust the time of last use if necessary, and any ratings reported more than four hours after MJ use were not coded as post-use data. While this four-hour window was selected to capture the acute effects of MJ use on mood, the duration of MJ effects are likely related to a range of factors including, but not limited to the specific product used (i.e. high THC/low THC), amount and frequency of use, mode of use, and metabolism. It may therefore be an important consideration for future studies to explore whether the duration of MJ intoxication is related to the duration of reported symptom improvement by BPD participants.

Further, although this investigation examined the *acute* effects of MJ use in BPD patients, additional investigations should explore the potential long-term impact of MJ use on clinical state. It is of note that over the duration of the study, the overall average mood ratings for the MJBP and BP were not significantly different across any measure (except for the MADRS), which provides preliminary evidence that MJ use may not *directly* result in poorer clinical course. Higher levels of clinical severity previously reported in MJ-smoking BPD patients [4, 8, 11] may be a result of several factors, including a failure to inform clinicians of MJ use. As MJ may partially address mood-related symptoms, the pharmacotherapeutic regimen prescribed

by physicians may, as a result, be different from what would normally be prescribed. Additionally, any short-term improvement following MJ use may result in non-adherence with patients' prescribed medications, which could ultimately result in poorer long-term outcomes.

Due to the preliminary nature of the current study, the relationship between specific patterns or levels of MJ use and symptom improvement were not thoroughly investigated. In addition, all MJ using participants in the current study were chronic MJ users and results may therefore not be generalizable to more casual MJ users. Future investigations should consider the impact of frequency and amount of MJ smoked, as well as mode of use, and strain of MJ used on both cognition and symptomatology. In fact, several studies have shown promise for the alleviation of anxiety using MJ products that contain high levels of CBD [67–68]. Given that CBD is a non-psychoactive phytocannabinoid that has shown promise as an anxiolytic and anticonvulsant (often used to stabilize mood in patients with BPD), high CBD-containing products may afford more viable options than other cannabinoid-based treatments. Therefore, future studies should also aim to explore whether high-CBD relative to low-CBD strains have differential effects in BPD patients as well as other clinical populations.

Finally, it should be noted the current study design does not imply cause and effect, but rather shows a *relationship* between MJ use and mood improvement. Clinical trials will be needed in order to further investigate the potential for MJ and cannabinoid-containing products as a potential treatment for patients with BPD.

Conclusions

New legislation across the nation has increased the overall accessibility of MJ to the general public for both recreational and medical use. To date, 24 states and the District of Columbia have fully legalized medical marijuana and another 18 states have allowed the use of CBD-based products for medical use. Each state individually regulates the use of MMJ, and perhaps not surprisingly, a wide range of acceptable conditions are often listed as eligible for MMJ certification. While some states include a “catchall” category, allowing physicians to certify conditions at their discretion, other states employ a restrictive list of indications suitable for MMJ. Additional studies are needed to help shape public policy regarding conditions that may be amenable to MMJ treatment, especially with regard to psychiatric illnesses. The current study highlights preliminary evidence that patients with BPD who regularly smoked MJ reported at least short-term clinical symptom alleviation following MJ use, indicating potential mood-stabilizing properties of MJ in at least a subset of patients with BPD. Furthermore, despite previous research showing that MJ use and BPD individually can have a negative impact on cognition, MJ use in BPD patients may *not* result in additional impairment. Further research is warranted to explore the impact of MJ on mood in clinical and non-clinical populations.

Supporting Information

S1 File. Manuscript Database. Demographic, cognitive, and EMA raw data, which were analyzed for the current manuscript, are available and arranged by group (HC, MJ, BP, and MJBP).
(XLSX)

Acknowledgments

The authors wish to thank Mr. Robert Baden for his administrative role, including grant preparation and submission.

Author Contributions

Conceived and designed the experiments: SG DO. Performed the experiments: SG MKD KS MD MR. Analyzed the data: SG MKD KS. Wrote the paper: KS SG MKD.

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JOURNAL OF
PSYCHOACTIVE DRUGS
A Multidisciplinary Forum



Journal of Psychoactive Drugs

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/ujpd20>

The Effect of Extreme Marijuana Use on the Long-Term Course of Bipolar I Illness: Single Case Study

Rif S. El-Mallakh^a & Carl Brown^b

^a Mood Disorders Research Program, Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, KY

^b Louisville Eccentric Observer, Louisville, KY

Published online: 08 Sep 2011.

To cite this article: Rif S. El-Mallakh & Carl Brown (2007) The Effect of Extreme Marijuana Use on the Long-Term Course of Bipolar I Illness: Single Case Study, *Journal of Psychoactive Drugs*, 39:2, 201-202, DOI: [10.1080/02791072.2007.10399879](https://doi.org/10.1080/02791072.2007.10399879)

To link to this article: <http://dx.doi.org/10.1080/02791072.2007.10399879>

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Short Communication

THE EFFECT OF EXTREME MARIJUANA USE ON THE LONG-TERM COURSE OF BIPOLAR I ILLNESS: A SINGLE CASE STUDY

Rif S. El-Mallakh, M.D.*
Carl Brown, J.D.**

Abstract—The effect of marijuana on bipolar disorder has never been systematically evaluated. Subjective reports by patients suggest an overall positive effect, but these may be unreliable. We herein report a case in which mood data was prospectively collected over two years of total substance abstinence and two years of extreme marijuana use. Marijuana use did not alter the total number of days of abnormal mood, however, marijuana was associated with an increase in the number of hypomanic days and a decrease in the number of depressed days. While not conclusive, the data suggest that marijuana may indeed have an effect on mood in bipolar patients that needs to be systematically examined.

Keywords—bipolar disorder, manic-depression, marijuana, prospective mood ratings

Marijuana use is quite common in patients with bipolar illness (Goldberg et al. 1999) but its effect on the course of bipolar illness is not clear (Tondo et al. 1999; Grinspoon & Bakalar 1998). There have not been any systematic evaluations of objective or subjective consequences of marijuana in bipolar disorder. Recently, the authors had the opportunity to examine the effect of chronic marijuana use in a Type I bipolar individual keeping meticulous daily mood charts.

CASE REPORT

Mr. B is a 53-year-old man, a former practicing attorney with a history of bipolar illness since age 26. He

*Director, Mood Disorders Research Program, Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, KY.

**Columnist, Louisville Eccentric Observer, Louisville, KY.

Please address correspondence and reprint requests to Rif S. El-Mallakh, M.D., Mood Disorders Research Program, Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, Kentucky 40202.

has maintained a daily mood chart for over 15 years. Mr. B utilized marijuana on a daily basis (maintaining a constant state of intoxication with 10 joints or equivalent daily). In 2000, Mr. B was imprisoned for a crime committed during a manic period. His sentence mandated 12 months in federal prison and a one-year probationary period during which he did not use any marijuana. However, immediately after the end of the probation, Mr. B reinstated his daily marijuana use. Mood charts for the four years (two years off marijuana and two years on marijuana) were prospectively recorded using the National Institute of Mental Health self-rating chart (a -4 to +4 scale). During most of these four years, pharmacologic management was kept constant, consisting of carbamazepine (1400 mg daily), lamotrigine (550 mg daily), and clonazepam (1 mg daily).

During the two years on marijuana use, Mr. B experienced 299 depressed days (41.0%, modal score -4), and 171 hypomanic days (23.4%, modal score +1). Depression was significantly less while using marijuana than the two years off marijuana (391 depressed days, 53.5%, modal score -4, $z = 5.0$, $P < 0.01$). Similarly, the hypomania occupied significantly greater time while using marijuana than off (111 hypomanic days, 15.2%, modal score +1, $z = 3.9$, $P < 0.01$). If the year in jail is excluded, and the year on probation is compared to the subsequent year, the results are not significantly different. Total number of depressed days while using marijuana was nonsignificantly less than the total number off marijuana (139 [38.1%] vs. 160 days [43.8%], respectively, $z = 1.58$, ns), while the total number of hypomanic days was significantly greater while using marijuana (104 [28.5%] vs. 67 [18.4%] days, $z = 3.26$, $P < 0.01$). The total number of ill days was not different (243 days while using marijuana vs. 227 days off marijuana, $z = 1.19$, ns). There were no full manic episodes in the entire four-year period.

DISCUSSION

This anecdotal prospective evaluation of the comparative effect of marijuana on the long-term course of bipolar illness suggests that heavy use is associated with a statistically significant reduction in depressed time and a significant increase in hypomanic days compared to abstinence. It is of interest that when marijuana is associated with psychosis, it frequently presents with manic or hypomanic features (Chaudry et al. 1991; Rottanburg et al. 1982). Anecdotally, patients report that marijuana use provides subjective mood

stabilization (Grinspoon & Bakalar 1998) or antidepressant effect (Gruber, Pope & Brown 1996).

In this case marijuana was not mood stabilizing since the total number of ill days did not change. However, the relative decline in depressed days and increase in hypomanic days was felt subjectively as an antidepressant effect by the patient. The apparent hypomanic promoting effect is consistent with previous clinical reports (Chaudry et al. 1991; Rottanburg et al. 1982).

There are clearly problems with this case. The two years in which the subject abstained from marijuana were marked by imprisonment and probation—both of which

could have an adverse effect on mood. However, the pattern of depression and hypomania revealed the same cycling that had gone on before imprisonment and after the end of probation, suggesting that this did not play an overt role.

Despite these considerations, this report suggests that preconceived notions that marijuana is depressogenic may need to be reexamined regarding its effect in bipolar patients. Similarly, the patient-promoted view that marijuana is mood stabilizing also needs to be reexamined. Clearly, larger studies would be important and potentially enlightening.

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Pros and Cons of Medical Cannabis use by People with Chronic Brain Disorders

Uma Suryadevara¹, Dawn M. Bruijnzeel¹, Meena Nuthi¹, Darin A. Jagnarine¹, Rajiv Tandon¹ and Adriaan W. Bruijnzeel^{1,2,3,*}

¹Department of Psychiatry, University of Florida, Gainesville, FL, USA; ²Department of Neuroscience, University of Florida, Gainesville, Florida, USA; ³Center for Addiction Research and Education, University of Florida, Gainesville, FL, USA

Abstract: Background: Cannabis is the most widely used illicit drug in the world and there is growing concern about the mental health effects of cannabis use. These concerns are at least partly due to the strong increase in recreational and medical cannabis use and the rise in tetrahydrocannabinol (THC) levels. Cannabis is widely used to self-medicate by older people and people with brain disorders such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), bipolar disorder, and schizophrenia.

Objective: This review provides an overview of the perceived benefits and adverse mental health effects of cannabis use in people with ALS, MS, AD, PD, bipolar disorder, and schizophrenia.

Results: The reviewed studies indicate that cannabis use diminishes some symptoms associated with these disorders. Cannabis use decreases pain and spasticity in people with MS, decreases tremor, rigidity, and pain in people with PD, and improves the quality of life of ALS patients by improving appetite, and decreasing pain and spasticity. Cannabis use is more common among people with schizophrenia than healthy controls. Cannabis use is a risk factor for schizophrenia which increases positive symptoms in schizophrenia patients and diminishes negative symptoms. Cannabis use worsens bipolar disorder and there is no evidence that bipolar patients derive any benefit from cannabis. In late stage Alzheimer's patients, cannabis products may improve food intake, sleep quality, and diminish agitation.

Conclusion: Cannabis use diminishes some of the adverse effects of neurological and psychiatric disorders. However, chronic cannabis use may lead to cognitive impairments and dependence.

ARTICLE HISTORY

Received: June 11, 2016
Revised: August 26, 2016
Accepted: October 28, 2016

DOI:
10.2174/1570159X14666161101095325

Keywords: Cannabis, dependence, cognition, neurological disorders, schizophrenia, bipolar disorder.

1. INTRODUCTION

Cannabis is one of the most widely used illicit drugs in the world. The United Nations Office on Drugs and Crime estimates that worldwide 3-5% of adults use cannabis [1]. The prevalence of cannabis use is very high in countries such as Ghana (21.5%), Zambia (17.7%), Canada (17.0%), the United States of America (US, 12.3%), and New Zealand (13.3%) [1]. It has been estimated that there are 20 million cannabis users in the US, including 1.2 million medical cannabis users [2, 3]. About 6 percent of Americans above the age of 18 will meet the DSM-5 criteria for cannabis use disorder at some point in their life [4].

In the US, federal law does not allow recreational or medical cannabis use. However, recreational and medical

cannabis use is legal in an increasing number of states. Twenty-three states and the District of Columbia have legalized the medical use of cannabis and 4 states have legalized its recreational use. It is expected that cannabis use will continue to increase as there is growing tolerance towards the use of cannabis and an increase in the number of patients who use cannabis for medical purposes [5]. Most cannabis studies have investigated the effects of cannabis in healthy adolescents and young adults. However, cannabis is also used recreationally by older adults and by patients with neurological and psychiatric disorders to alleviate symptoms associated with their disorder. A large study with participants from 31 countries showed that 24.1% of cannabis users are between the ages of 51 and 60, 5.8% between 61 and 70, and 0.6% are older than 70 [6]. Cannabis use has more than quadrupled among the 55-59 year olds (1.6 to 7.4%) and doubled among 60-64 year olds (2.4 to 4.4%) between 2002 and 2012 [7].

In addition to the increase in cannabis use in the elderly, there has also been an increase in the use of cannabis for the

*Address correspondence to this author at the University of Florida, College of Medicine, Department of Psychiatry, 1149 Newell Dr. Gainesville, FL, USA 32611; Tel: 352-294-4931; E-mail: awbruijn@ufl.edu

treatment of neurological disorders [8, 9]. This is in combination with the dramatic increase in THC levels in cannabis which could lead to an increase in the number of people who experience adverse mental health effects [10]. In addition to cannabis, cannabis-based treatments such as nabiximols (trade name Sativex, cannabis plant extract, 1:1 ratio of CBD:THC), dronabinol (trade name Marinol, synthetic THC), and nabilone (trade name Cesamet, synthetic cannabinoid with chemical structure similar to THC) have also been used by people with brain disorders. Both nabilone and dronabinol have been approved by the US Food and Drug Administration (FDA) for the treatment of nausea and vomiting associated with chemotherapy for cancer and to stimulate appetite in AIDS patients with wasting syndrome. Nabiximols is already being used in 15 countries for the treatment of spasticity associated with multiple sclerosis (MS) and in the US, Sativex is being reviewed by the FDA for the treatment of cancer pain. The goal of this review is to provide insight into the potential beneficial and harmful effects of cannabis use and cannabis-based treatments in people with common neurological or psychiatric disorders and older individuals.

2. CANNABINOIDS

Cannabis has been used in religious ceremonies and for medical purposes for thousands of years [11]. Cannabidiol (CBD), the main non-psychoactive component of cannabis, was isolated in the 1940s and its structure was established in the 1960s [12, 13]. It wasn't until 1964 that tetrahydrocannabinol (THC) was isolated [14]. Cannabidiol does not induce intoxication and diminishes the psychotropic effects of THC [15, 16]. The cannabinoids can be classified into three groups: phytocannabinoids, endocannabinoids, and synthetic cannabinoids [17]. More than one hundred phytocannabinoids have been isolated but in most commercial cannabis strains, only THC is produced in high levels [18]. Another phytocannabinoid that is sometimes expressed at high levels is CBD. Furthermore, two endocannabinoids have been discovered, namely 2-arachidonoyl glycerol (2-AG) and anandamide [19-21]. Some synthetic cannabinoids have a much higher potency than THC and have been associated with severe adverse mental health effects [22]. Cannabinoids mediate their effects *via* the activation of the cannabinoid type 1 (CB₁) and type 2 (CB₂) receptor. The endogenous ligands for these receptors are 2-AG and anandamide. The CB₁ receptor is one of the most common receptors in the central nervous system. High levels of CB₁ receptors have been detected in the hippocampus, basal ganglia, prefrontal cortex and cerebellum [23]. The localization of this receptor in the basal ganglia, hippocampus, and prefrontal cortex underscores the critical role of the cannabinoid system in the regulation of motor function and cognition [24]. The CB₂ receptors are mostly found in the periphery (thymus and spleen), but they have also been detected on cerebellar and brain stem neurons [25]. Cannabinoid type 2 receptor levels are extremely low in the healthy brain but their levels increase after injury and inflammation [26, 27]. The CB₂ receptors are mainly expressed on activated microglia, which play a critical role in the removal of dying cells but also induce the release of cytotoxic molecules that can lead to cell

death [28, 29]. Activation of the CB₂ receptor decreases the release of cytokines and chemokines and diminishes inflammation and cell death [30, 31].

3. ANIMAL STUDIES

Studies with animals have provided evidence for the fact that chronic exposure to cannabis smoke, tetrahydrocannabinol (THC), or CB₁ receptor agonists leads to the development of dependence. Cannabis withdrawal leads to somatic withdrawal signs (*e.g.*, abdominal constriction, wet-dog shakes, head shakes, forepaw fluttering), anxiety-like behavior, and an increased release of the stress peptide corticotropin-releasing factor in the amygdala [32-35]. The negative affective state associated with drug withdrawal provides powerful motivation for the continuation of drug use [36, 37]. There is also extensive evidence that cannabis and THC impair memory and cognition in rodents. The eight-arm radial maze is a well validated test for investigating the neuronal mechanisms that underlie memory [38]. Nakamura *et al.* demonstrated that THC disrupts working memory in the radial maze test [39]. THC inhibits the release of acetylcholine in the hippocampus and this is likely one mechanism by which it impairs memory. This is supported by the observation that drugs that prevent the THC-induced decrease in acetylcholine release in the hippocampus also prevent memory impairments [40]. It has also been suggested that repeated THC administration leads to increased glutamate levels, which induces a downregulation of glutamate receptors and a reduction in the density of dendritic spines on hippocampal neurons. This may reduce synaptic plasticity and thereby cause memory impairments [41]. Memory impairments due to THC exposure may gradually diminish over time. In the above mentioned study by Nakamura *et al.*, memory function returned to baseline levels after 4 weeks of abstinence [39]. Another study reported that memory function in mice was still impaired three weeks after the administration of one low dose of THC [42]. Therefore, this suggests that the memory function might recover after cannabis use, but only after an extended amount of time.

4. ACUTE EFFECTS OF CANNABIS USE

Cannabis has a wide range of subjective effects. The effects may vary between light and heavy users and can include feelings of intoxication, euphoria, altered sensory perception, cognitive and perceptual distortions, anxiety, dizziness, and increased appetite [43]. The most reliable markers of acute cannabis exposure are intoxication and tachycardia [44]. In terms of cognitive processes, there is extensive evidence that acute cannabis exposure impairs attentional tasks, consolidation and retrieval of memory, working memory, verbal memory, learning, and executive functions [44]. Impaired performance has been consistently found in multiple aspects of attention, including sustained attention, divided attention, selective, and focused attention [45]. Additionally, studies have found executive dysfunction related to cannabis exposure, including disinhibition and impaired decision making [46]. Acute cannabis intoxication in healthy young people causes slower reaction times, impaired accuracy, and impaired response inhibition [47, 48]. Other frontal dysfunction that has been observed

includes decreased information processing speed, poor planning, lack of self-monitoring, and inability to alter behaviors to suit changing tasks [49-51]. There can also be alterations in mathematical abilities and time perception, along with changes in the gross and fine motor skills [52, 53]. Taken together, these studies indicate that acute cannabis use affects emotional states and dramatically impairs cognitive processes and motor functions.

5. CHRONIC EFFECTS OF CANNABIS USE

One of the main adverse effects of cannabis use is the development of dependence. In the US, almost 10% of adults use cannabis and one third users meet the criteria for cannabis use disorder [54]. Cannabis use disorder is characterized by a strong desire to use cannabis, using larger amounts than intended, and continued usage despite negative social and physical consequences, craving, tolerance and withdrawal [55]. It has been estimated that 30% of regular cannabis users and 50-95% of heavy users experience a cannabis withdrawal syndrome [56]. Cannabis withdrawal is characterized by anxiety, depression, irritability, decreased sleep quality along with the quantity and stomach pain [57, 58]. This negative affective state plays a critical role in the maintenance of drug addiction [37]. Studies that have evaluated the long term effects of cannabis use on cognition are sparse. In one study in which participants were followed from birth to age 38, persistent cannabis users had a 6 point reduction in IQ compared to non-users [59]. Some longitudinal studies have shown persistent adverse effects of cannabis use on neurocognitive performance. These effects depend on the length of abstinence, age at the onset, or cumulative lifetime exposure [60]. Significant psychomotor dysfunction has also been reported in chronic cannabis users [61]. Some recovery of cognitive function might occur after cessation of cannabis use. Adolescent cannabis users with 3 weeks of sobriety demonstrated resolution of learning and verbal memory deficits, but continued to have difficulty with attentional tasks [62]. In one longitudinal study in young adults, episodic memory improved over an eight year abstinence period [63]. Taken together, this indicates that chronic cannabis use can lead to loss of control over cannabis use and cognitive impairments, which may diminish gradually after a prolonged abstinence period. Chronic cannabis use can also lead to what is called an amotivational syndrome [64, 65]. This amotivational syndrome is characterized by apathy, lack of motivation, and poor educational performance. Animal studies suggest that the amotivational syndrome is due to a THC-induced dysregulation of dopaminergic systems [66]. This is supported by a study with human cannabis users that showed that cannabis users with the highest level of apathy had the lowest dopamine synthesis capacity in the striatum [67].

6. STRUCTURAL CHANGES IN CANNABIS USE

There is extensive evidence for structural and functional abnormalities in young cannabis users. Chronic cannabis use leads to changes in gray (cell bodies, dendrites, and synapses) and white matter (myelinated neuronal tracts) architecture [68, 69]. There is some evidence that cannabis use may increase the volume of subregions of the cerebellum

and amygdala in adolescents [70, 71]. The changes in the volume of these brain sites were associated with poor executive functioning (cerebellum) and internalizing problems (amygdala) [70, 71]. An increase in the volume of a brain site might be due to disrupted pruning of gray matter during a critical period in adolescence or possibly abnormal connectivity patterns that develop to compensate for cognitive deficits [72]. Although some studies reported that cannabis use can increase the size of brain regions, the great majority of the studies found that cannabis use decreases the volume of brain regions. Cannabis use-induced decreases in brain volume have been reported for the orbitofrontal cortex, hippocampus, striatum, and amygdala [69, 73-76]. One of the most consistent findings has been that cannabis use decreases the volume of the hippocampus and this correlates with the amount of cannabis used and the level of dependence [77]. It should be noted that a recent study reported that daily cannabis use does not affect the volume of the nucleus accumbens, amygdala, hippocampus, or cerebellum [78]. It was suggested that there was no effect of cannabis use on brain volumes because the study closely controlled for other factors that may affect the volume of specific brain sites, such as alcohol use. Taken together, conflicting findings about the effect of cannabis use on the volume of brain sites have been reported. Some of these differences might be due to difference in study design, comorbid drug use, and data analysis. Well controlled animal studies with young and old animals are urgently needed to evaluate the effects of cannabis smoke exposure on the volume of specific brain regions.

Cannabis use is most common among adolescents and young adults and this period is also critical for brain myelination. Cannabinoid receptors are found on myelinating glial cells and are thought to play a role in white matter integrity and connectivity [79]. A number of studies that investigated neuronal tracts in the brain using diffusor tensor imaging have found reductions in white matter integrity throughout the frontal and temporal lobes in adolescent cannabis users [68, 80-82]. These abnormalities are associated with psychological symptoms and cognitive impairments. Chronic cannabis use also leads to impairments in cerebrovascular functioning, which has been associated with an increased risk for stroke [83, 84]. There is a lack of data regarding the effects of cannabis use on the brain of the elderly. The vast majority of cannabis studies have been conducted with young adults. Given the rapid increase in the aging population, it is critical to gain a better understanding of the acute and long-term effects of cannabis use in this group.

7. CANNABIS AND AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that rapidly progresses and primarily affects the motor neurons in the spinal cord and brain stem. One of the first symptoms is muscle weakness in one part of the body, which then spreads to other parts. Furthermore, thirty to fifty percent of ALS patients have signs of cognitive impairments [85, 86]. Amyotrophic lateral sclerosis is very rare in people before the age of 40, and the median age at diagnosis is 65 for males and 67 for females

[87]. The precise cause of ALS is unknown. However, several possible causes for ALS have been identified: 1) oxidative damage, 2) blockade of axonal transport by neurofilaments, 3) toxicity from intracellular aggregates, and 4) glutamate-mediated excitotoxicity [88]. Although it is not known what causes ALS, there is strong evidence that inflammation plays a role in its progression [89]. Amyotrophic lateral sclerosis has been associated with changes in the endogenous cannabinoid system and cannabinoid receptor agonists may slow down the progression of ALS by decreasing inflammation. Animal studies have shown that endogenous cannabinoid levels are elevated in spinal cord of symptomatic ALS mice [90]. Interestingly, CB₂ receptors, but not CB₁ receptors, are upregulated in a mouse model for ALS (G93A-SOD1 mutant mice) [91]. This observation is in line with a recent study in which CB₁ and CB₂ receptor levels were assessed in TAR-DNA binding protein-43 (TDP-43) mice [92]. These mice are considered an animal model for ALS [93]. TDP-43 aggregates have been detected in the brains of ALS patients and it has been suggested that these aggregates induce toxicity and cell death [94, 95]. Interestingly, in both male and female TDP-43 mice there is an upregulation of CB₂, but not CB₁, receptors in the spinal cord [92]. Treatment with THC, the synthetic CB₁ and CB₂ receptor agonist WIN55,212-2, and the selective CB₂ agonist AM-1241 delays ALS progression in animal models [91, 96]. Furthermore, the neuroprotective effects of THC are diminished by CB₁ receptor blockade [97]. Taken together, this suggests that both CB₁ and CB₂ agonists may slow down the progression of ALS.

Cannabinoids target multiple neuronal pathways and exert anti-inflammatory and neuroprotective effects. A post-mortem study showed that ALS patients have elevated CB₂ receptor levels on microglia in the spinal cord [98]. Unfortunately, CB₁ receptor levels were not assessed in the aforementioned study, but studies with animal models for ALS suggest that ALS is not associated with an upregulation of CB₁ receptors [91, 92]. Microglia do not express CB₂ receptors under baseline conditions but neuronal damage leads to microglia activation and the expression of CB₂ receptors [99].

Clinical studies suggest that cannabis may improve ALS symptoms. There is evidence that cannabis helps with pain, spasticity, drooling, appetite loss, and sleep [100, 101]. In patients with respiratory failure due to ALS, cannabis may help by inducing bronchodilation [102, 103]. Overall, these studies suggest that cannabis diminishes ALS symptoms and thereby improve the quality of life of patients. Clinical studies indicate that ALS is associated with high levels of anxiety and depression [104-106]. Small amounts of cannabis may help people to relax, induces euphoria, and decreases anxiety and thereby could also increase the quality of life of ALS patients [107-109]. Overall, the reviewed studies suggest that cannabis use may diminish some of the symptoms associated with ALS and delay disease progression (See Table I for an overview).

8. CANNABIS AND MULTIPLE SCLEROSIS

Multiple Sclerosis is a chronic demyelinating disease of the central and peripheral nervous system [110, 111]. The symptoms (*e.g.*, vision problems, muscle weakness, pain,

balance problems, and paralysis) are due to uncontrolled or inappropriate neural transmission that gradually worsens when the disease progresses. During the early stage of the disease, patients may experience long periods during which they are relatively symptom free and these periods are interrupted by flare ups that lasts days to weeks. It has been suggested that cannabis, THC, nabiximols, and oral cannabis extract (OCE) may diminish spasticity associated with MS [112]. Thus far, one cannabis based drug (nabiximols) has been developed for the treatment of MS. Nabiximols is a mucosal spray that contains THC and CBD in a 1:1 ratio. The US FDA has approved nabiximols for clinical trials and it has been approved in several European countries, Canada, and New Zealand for the treatment of spasticity associated with MS.

Animal studies show that cannabinoid receptor agonists diminish tremors and spasticity in mouse models for MS [113]. Preclinical studies suggest that spasticity associated with MS is diminished by CB₁, but not CB₂, receptor agonists [114]. Cannabinoids have neuroprotective effects due to their action on microglial cells [115, 116]. Medical cannabis has been shown to decrease spasticity and pain in MS patients but it has negative effects on posture and balance [117, 118]. Furthermore, both nabiximols and THC decrease spasticity in MS patients [119, 120]. Oral cannabis extract has proven to be very effective for the treatment of central pain [119]. In addition to this, people with MS often suffer from severe bladder dysfunction due to the disruption of neuronal transmission between the brain and bladder. Some evidence suggests that nabiximols, but not dronabinol or oral cannabis extract, improves bladder function in people with MS [119, 121]. The cannabis based treatments did not reduce tremors in patients with MS [119, 122].

Multiple sclerosis has been associated with cognitive impairments, depression, and anxiety [123, 124]. It has been estimated that about 50% of MS patients have cognitive deficits and suffer from depression [125-127]. Multiple Sclerosis patients who smoke cannabis have more severe cognitive impairments than nonusers [128, 129]. Patients with MS who smoke cannabis perform poorly on tests for information processing speed, working memory, executive functioning, and visuospatial perception compared to ALS patients who do not smoke cannabis [129]. Multiple sclerosis patients who used cannabis were also twice as likely to be considered cognitively impaired [129]. Furthermore, in MS patients who use cannabis there is a correlation between cognitive impairments and reductions in gray and white matter volume in medial and lateral temporal regions, thalamus, basal ganglia, and prefrontal regions [130]. So far there is no evidence that cannabis use affects anxiety and depression in MS patients. Overall, the reviewed studies indicate that cannabis use may diminish spasticity and pain associated with MS, but chronic cannabis use has a detrimental effect on cognition in MS patients.

9. CANNABIS AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative brain disorder that decreases quality of life as it leads to bradykinesia (slow movements), rigidity, and tremors. Parkinson's has also been associated with non-motor symptoms that may

Table 1. Cannabis based treatments and expression of disease symptoms.

Disorder / Drug	Effect on Symptoms	Type of Study	Refs.
ALS			
Cannabis (smoked)	Appetite (↑), anxiety and depression (↓), Pain (↓), spasticity (↓), muscle relaxation (↑), drooling (↓), sleep (↑).	Survey	[101, 222]
THC (synthetic, dronabinol, drops)	Cramp intensity (=)	Clinical study	[223]
MS			
Cannabis (smoked)	Spasticity (↓), Pain (↓)	Clinical study	[117]
THC/CBD (nabiximols, oral spray)	Spasticity (↓), Pain (↓)	Clinical studies	[120, 224, 225, 226, 227]
THC (plant extract, oral capsule)	Muscle stiffness (↓)	Clinical study	[228]
THC (synthetic, dronabinol, capsule)	Spasticity (↓), Pain (↓)	Clinical study	[119]
THC (synthetic, nabilone, oral capsule, adjunct to gabapentin)	Pain (↓)	Clinical study	[229]
Parkinson's disease			
Cannabis extract (oral capsules)	Levodopa-induced dyskinesia (=), Parkinson's motor symptoms (=).	Clinical study	[142]
Cannabis leaves (oral leaves)	Rigidity (↓), bradykinesia (↓), resting tremor (↓), levodopa-induced dyskinesia (↓)	Survey	[138]
Cannabidiol	Quality of life (↑)	Clinical study	[230]
THC (synthetic, nabilone, oral capsule)	levodopa-induced dyskinesia	Clinical study	[141]
Alzheimer's disease			
THC (dronabinol, synthetic THC, oral capsule)	Agitation (↓), food intake (↑), sleep duration (↑)	Clinical study	[154]
THC (dronabinol, synthetic THC, oral capsule)	Disturbed behavior (↓), body weight gain (↑)	Clinical study	[155]
THC (dronabinol, synthetic THC, oral capsule)	Nocturnal motor activity (↓), agitation (↓), appetite disturbances (↓), irritability (↓)	Clinical study	[156]
THC (nabilone, synthetic)	Agitation (↓), resistance during care (↓)	Case report	[231]
Schizophrenia			
Cannabidiol	All schizophrenia symptoms (Brief Psychiatric Rating Scale) (↓)	Case report	[232]
Cannabidiol	Positive and negative symptoms (↓)	Clinical study	[185]
Bipolar disorder	Not evaluated in clinical studies		

include psychosis, cognitive impairments, anxiety, and depression [131]. Parkinson's symptoms are at least partly due to the loss of dopaminergic neurons in the substantia nigra, which leads to a dysregulation of the extrapyramidal system. There is evidence that the endocannabinoid system is dysregulated in PD patients. It should be noted, however, that at this point it is not known if a dysregulation of the endocannabinoid system contributed to the development of PD or that PD leads to changes in the endocannabinoid system. Patients with PD have elevated levels of anandamide in the cerebrospinal fluid (CSF) and decreased CB₁ receptor levels in the basal ganglia [132, 133]. Animal studies suggest that drugs that target the cannabinoid system might diminish

PD's motor symptoms and slow disease progression. In a Marmoset PD model, THC improved both activity and hand-eye coordination [134]. The phytocannabinoid Δ⁹-tetrahydrocannabinol (THCV; CB₁ receptor antagonist and CB₂ receptor agonist) attenuates motor inhibition in the 6-hydroxydopamine (6-OHDA) model of PD [135]. Furthermore, the cannabinoids THC and CBD diminish the neurotoxic effects of 6-OHDA, and these effects might be mediated by their antioxidant or anti-inflammatory properties [136]. In the same animal model, a drug treatment (AM404) that enhanced anandamide levels also decreased PD symptoms [137]. Therefore, there is strong preclinical evidence that increasing cannabinoid tone diminishes PD symptoms.

Clinical studies suggest that cannabis may diminish the motor symptoms associated with PD [138, 139]. A small study with 22 patients showed that smoking cannabis improves motor symptoms such as resting tremor, rigidity, bradykinesia, and posture. In the same study, cannabis also decreased pain and improved sleep quality [139]. It has also been reported that CBD diminishes REM sleep behavior disorder in people with PD [140]. Furthermore, the synthetic cannabinoid receptor agonist nabilone attenuates levodopa-induced dyskinesia in PD patients [141]. Oral cannabis extract or CB₁ receptor blockade with rimonabant does not improve motor symptoms associated with PD [142, 143]. Overall, clinical studies suggest that cannabis, CBD, and synthetic cannabinoid agonists may diminish motor symptoms and pain associated with PD. At this point, only a few relatively small studies have been conducted and additional studies are needed before firm conclusions can be drawn about the effect of cannabis on PD. Furthermore, before medical cannabis can be recommended to PD patients, clinical studies are needed to investigate the effects of cannabis on non-motor systems (hallucinations, cognitive impairments) associated with PD.

10. CANNABIS AND ALZHEIMER'S DISEASE

Neurocognitive disorders are increasingly prevalent in the aging population. Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder. Alzheimer's is truly a brain disease of the elderly; 4.3% of the 75-80 year olds and 28.5% of the 90 year olds has been diagnosed with AD [144]. The majority of AD patients are between the ages of 80 and 85. One of the first clinical symptoms is memory impairment and this is followed by language and behavioral problems. Alzheimer's is characterized by the loss of synapses and lesions that include plaques composed of an amyloid (A β) core and neurofibrillary tangles that mainly consist of hyperphosphorylated tau [145]. Alzheimer's has significant effects on the expression of CB₂ receptors in the human brain. One study reported a high level of CB₂ receptor expression in microglia associated with β -amyloid-enriched neuritic plaques while CB₂ receptors were not detected beyond the borders of the plaques or in the brains of healthy controls [146]. In contrast, AD does not lead to changes in CB₁ receptor levels [146, 147]. The therapeutic effects of the cannabinoids are hypothesized to be due to their antioxidant, anti-inflammatory, and neuroprotective effects, which may diminish the effects of beta-amyloid toxicity [148, 149]. Animal studies indicate that compounds that elevate endocannabinoid levels decrease the toxic effects of beta-amyloid peptide [150]. Furthermore, studies with an AD mouse model (amyloid-protein precursor/presenilin 1) show that a THC-CBD mixture decreases amyloid beta levels and reverses learning impairments [151]. In the same animal model, a CB₂ receptor agonist improves cognition, decreases tau hyper-phosphorylation, and decreases the expression of pro-inflammatory cytokines [152]. Therefore, cannabinoid based treatments could potentially slow the progression of AD.

Cannabis might also be effective for the treatment of late stage AD symptoms [153]. Several studies have investigated the effects of dronabinol, which is a synthetic version of

THC, in late stage AD patients. These studies showed that dronabinol improves food intake, sleep duration, circadian rhythm, and decreases agitation in late stage AD patients [154-157]. The patients received dronabinol for only a short period of time and it was not investigated if dronabinol affects memory and cognition. Therefore, additional studies are needed to investigate the long-term cognitive effects of THC or THC-like compounds in AD. Overall, these studies suggest that cannabis may slow down the progression of AD and decreases some its symptoms. However, additional insight into the effects of cannabis on cognition in AD patients is needed.

11. CANNABIS AND BIPOLAR DISORDER

Bipolar disorder is characterized by major depressive and manic episodes or episodes with mixed depressive and manic symptoms [55]. Cannabis is the most often used illicit drug in patients with bipolar disorder and people with bipolar are seven times more likely to use cannabis than controls [158, 159]. It was initially believed that cannabis might have some therapeutic effects in bipolar patients, but this is not supported by recent findings [160]. Cannabis use is associated with an early age of onset of bipolar disorder, increased severity, and increased disability [161-163]. Cannabis use in patients with bipolar also further increases the risk for suicide [159]. A prospective study showed that cannabis use is associated with a decrease in long-term remission for bipolar disorder [164]. A large epidemiological study indicated that cannabis use increases the risk for manic symptoms [165]. Cannabis also worsens global functioning in patients with bipolar disorder [166]. There is no indication for CB₁ receptor level changes in people with bipolar disorder [167]. However, a single nucleotide polymorphisms in the CB₂ receptor gene (SNP, rs41311993, 524C>A; Leu133Ile) is more common in people with bipolar disorder than in healthy controls [168]. This gene has been associated with CB₂ receptor stability and therefore changes in the CB₂ receptor could possibly contribute to the development of bipolar disorder. Finally, cannabis may alter the metabolism of medications prescribed for bipolar disorder. Overall, there are no clear indications that bipolar patients derive a benefit from cannabis use.

12. CANNABIS AND SCHIZOPHRENIA

Schizophrenia is a mental disorder that typically presents in late adolescence or early adulthood and is among the top ten leading causes of disability in the world [169]. Schizophrenia is characterized by three core symptom groups: positive symptoms (hallucinations, delusions, grandiosity, paranoia, and suspiciousness), negative symptoms (blunted affect, social avoidance, poor rapport, lack of motivation, lack of spontaneity, and emotional withdrawal), and cognitive dysfunction [170]. Cannabis use is more common among people with schizophrenia than in the general population [171]. In Western countries, 10%20% of the general population use cannabis while 30%50% of people with schizophrenia use cannabis [172, 173]. There are several possible explanations for this. Cannabis might be more rewarding in people with schizophrenia, it might compensate for brain deficits, or people with schizophrenia have less control over drug use.

There is extensive evidence that the endogenous cannabinoid system is dysregulated in people with schizophrenia. Anandamide levels are elevated in the CSF of schizophrenia patients [174]. Furthermore, post mortem studies have shown an increase in CB₁ receptor levels in schizophrenia patients, especially in the dorsolateral prefrontal cortex, pons, cingulate cortex, and nucleus accumbens [175-180].

There is extensive evidence that cannabis use increases the risk for schizophrenia [181]. A large study with 50,087 Swedish men showed that cannabis users are 7 times more likely to develop schizophrenia than people who do not use cannabis [182]. This is in line with another large study that reported an increase in cannabis use in people in the year before they were first diagnosed with schizophrenia [183]. It should be noted that the harmful effects of cannabis depend on the THC:CBD ratio [181]. THC increases the risk for psychosis but CBD diminishes the effects of THC and even has antipsychotic effects in people with schizophrenia [184, 185]. During the last decades there has been an increase in THC levels in cannabis and CBD levels have remained the same. From 1980 to 2008, the THC concentration in cannabis products increased from 3 to 9 % while CBD levels remained stable at 0.4 % [186]. This suggests that cannabis use is more likely to lead to psychiatric illness and in particular in people who are genetically predisposed to develop schizophrenia [187, 188].

It is interesting to note that electroencephalography (EEG) studies have revealed that chronic cannabis use disrupts the brain's ability to generate synchronized neuronal oscillations (beta and gamma band activity) [189, 190]. Neuronal oscillations play a critical role in coordinating the activity between brain sites and a disruption in synchronized neuronal activity can affect a wide range of brain functions. Chronic cannabis use induces similar disruptions in neuronal synchronization as those observed in people with schizophrenia [191]. Therefore it has been suggested that cannabis' effect on neuronal oscillations may contribute to the development of schizophrenia (for an extensive review on this topic see [191, 192]).

Cannabis use has a detrimental effect on some schizophrenia symptoms. Cannabis use worsens positive symptoms (mainly hallucinations), leads to poor treatment outcomes, and increases the risk for relapse after a period of remission [193-196]. It has been suggested that cannabis use disrupts the endogenous cannabinoid system in the prefrontal cortex and thereby induces changes in glutamate and GABA release, which contributes to the development of schizophrenia [197]. The effects of cannabis use on dopaminergic systems might also play a role in the development of schizophrenia. The catechol-O-methyltransferase (COMT) gene plays an important role in the breakdown of dopamine, and a valine to methionine mutation (Val¹⁵⁸Met) in this gene leads to a decrease in dopamine metabolism [198]. It has been suggested that this mutation by itself does not increase the risk for schizophrenia but increases the risk for schizophrenia in people who use cannabis [199]. There is some evidence that cannabis use may diminish the negative symptoms of schizophrenia. Several small studies suggest that a majority of people with schizophrenia use cannabis to diminish negative symptoms [200, 201].

The adverse effects of cannabis use might be more severe for people with schizophrenia than for healthy controls [202]. Cannabis use leads to a larger decrease in gray matter volume in people with schizophrenia than in healthy controls [202]. Interestingly, the decrease in gray matter volume was greatest in brain areas with high levels of CB₁ receptors such as the dorsolateral prefrontal cortex and the anterior cingulate cortex [203]. Despite the negative effect of cannabis use on gray matter volume in people with schizophrenia, several studies suggest that people with schizophrenia who use cannabis have better cognitive function than people with schizophrenia who do not use cannabis [204-208]. However, it has also been reported that people with schizophrenia who use cannabis have worse cognitive function than patients who do not use cannabis [209]. It should be noted that it might be possible that cannabis use does not improve cognition but that patients who use cannabis have less severe cognitive impairments than non-cannabis users. It has been hypothesized that cannabis use in vulnerable young people can lead to a type of schizophrenia that is characterized by psychosis and only mild cognitive impairments [208, 210]. In contrast, people who do not use cannabis and develop schizophrenia have psychotic symptoms and also severe cognitive impairments.

The endogenous cannabinoid system has been identified as a target for the treatment of schizophrenia [169]. Since the 1970's it has been suggested that the cannabinoid CBD has antipsychotic properties [211]. In the prepulse inhibition (PPI) paradigm in healthy humans, a weak pre-pulse inhibits the strong startle response caused by an intense stimulus (e.g., loud noise) [212]. However, this inhibitory response is disrupted in people with schizophrenia (*i.e.*, impaired PPI) [213]. Drugs that induce schizophrenia-like symptoms in humans such as the NMDA receptor antagonists MK-801 and ketamine also disrupt PPI in rats [212]. A wide range of antipsychotic drugs diminish the PPI impairment induced by NMDA receptor antagonists [214]. Interestingly, recent studies suggest that CBD also attenuates the PPI impairment induced by the NMDA receptor antagonist MK-801 or amphetamine [215-217]. This suggests that cannabis might mediate some effects that resemble those of antipsychotic drugs.

Taken together, cannabis has a complex effect on schizophrenia and the effect might depend on the THC and CBD levels in cannabis. Regular use of cannabis with high levels of THC has detrimental effects on gray matter and positive symptoms of schizophrenia. On the other hand, cannabis does not seem to worsen the cognitive symptoms associated with schizophrenia and might diminish some of the negative symptoms. Cannabis with high levels of CBD and low levels of THC could possibly prevent some of the deficits in sensory motor gating in patients with schizophrenia.

CONCLUDING REMARKS

The goal of this article is to provide an overview of the benefits and negative mental health effects of cannabis use by people with a neurological disorder, bipolar disorder, or schizophrenia. The reviewed studies indicate that cannabis use has complex effects and its effects depend on the specific brain disorder for which it is being used. Clinical studies

provide evidence that cannabis might diminish some of the symptoms associated with PD, ALS, and MS. Cannabis use may decrease spasticity and pain in people with MS, decrease tremor, rigidity, and pain in people with PD and improve the quality of life of ALS patients by improving speech and swallowing, and decreasing spasticity. There is also evidence that people with schizophrenia use cannabis to diminish some of the symptoms of their disorders. Cannabis use might temporarily improve the negative symptoms of schizophrenia. There is currently no evidence that people with bipolar disorder derive any benefit from cannabis. The acute and chronic effects of cannabis use in the elderly are poorly understood. Aging is associated with physiological and neurological changes that may affect the response to cannabis. Changes in lean and fat mass may affect the volume of distribution of THC, and impairments in THC clearance may lead to elevated drug levels and increased drug interactions [218, 219]. Cannabis has large effects on neurotransmitter release in the hippocampus and prefrontal cortex and these brain sites also undergo changes during aging [220, 221]. Because cannabis use in the elderly is on the rise, clinical and preclinical studies are urgently needed to investigate the physiological and neurological effects of cannabis use in the elderly.

Taken together, many people with PD, ALS, MS, and schizophrenia smoke cannabis to diminish the symptoms associated with their disorder. It should be noted that while short term use of cannabis could diminish some of the symptoms of these disorders, chronic cannabis use can have adverse long-term effects. It has been firmly established that chronic cannabis use can lead to the development of dependence, cognitive impairments, which increases the risk for depression and anxiety. Cannabis also has adverse physiological effects such as increasing the risk for lung diseases and has negative effects on male and female reproductive systems. Overall, acute cannabis use might provide temporary relief from a wide range of symptoms associated with neurological and psychiatric disorders, but prolonged heavy cannabis use might have adverse effects on mental and physiological health.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest. One of the authors (AB) was supported in part by an NIH grant (DA039349) when working on this review.

ACKNOWLEDGEMENTS

Declared none.

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RESEARCH ARTICLE

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Continued cannabis use at one year follow up is associated with elevated mood and lower global functioning in bipolar I disorder

Levi Roestad Kvitland^{1*}, Ingrid Melle¹, Sofie Ragnhild Aminoff^{1,2}, Christine Demmo¹, Trine Vik Lagerberg¹, Ole Andreas Andreassen¹ and Petter Andreas Ringen³

Abstract

Background: There is limited knowledge about how environmental factors affect the course of bipolar disorder (BD). Cannabis has been proposed as a potential risk factor for poorer course of illness, but the role of cannabis use has not been studied in a first treatment BD I sample.

Methods: The present study examines the associations between course of illness in first treatment BD I and continued cannabis use, from baseline to one year follow up. Patients (N = 62) with first treatment DSM-IV BD I were included as part of the Thematically Organized Psychosis study (TOP), and completed interviews and self-report questionnaires at both baseline and follow up. Cannabis use within the last six months at baseline and use between baseline and follow up ("continued use") was recorded.

Results: After controlling for confounders, continued cannabis use was significantly associated with elevated mood (YMRS) and inferior global functioning (GAF-F) at follow up. Elevated mood mediated the effect of cannabis use on global functioning.

Conclusions: These results suggest that cannabis use has clinical implications for the early course of BD by increasing mood level. More focus on reducing cannabis use in clinical settings seems to be useful for improving outcome in early phase of the disorder.

Keywords: Cannabis, Bipolar

Background

The prevalence of substance use in bipolar disorder (BD) is high [1-3] with cannabis being the most commonly used drug [3]. This is of interest since cannabis has been indicated as a risk factor for developing BD [4-6]. Cannabis use has also been associated with severity indicators in chronic BD, including earlier age of onset for the first affective episode [7-13], increased risk of manic episodes [4,14], prolonged duration of episodes [4-6], switch to mania in depressed individuals [15] and increased suicidal ideation and suicide risk [16,17], in addition to a more severe general course of the illness

[18-20]. Cannabis abuse has furthermore been shown to predict poorer medication adherence in BD patients [21]. Most of these studies have included patients mainly in the chronic phase of illness after multiple mood episodes, and we cannot rule out the possibility that these findings are biased by a selection of patients with a more severe course, possibly being more prone to self-medication with cannabis.

Longitudinal studies of BD samples recruited at first treatment are very few. Two follow-up studies of first time hospitalized patients with BD I indicate that patients with cannabis use spend more time in affective episodes and exhibit more rapid cycling over the first year of treatment [22], and that periods with cannabis use coincide with periods with manic and hypomanic episodes over a mean follow-up period of 4.5 years [6]. Both studies suggest that continued cannabis use in patients with recently

* Correspondence: l.r.kvitland@medisin.uio.no

¹NORMENT, KG Jebsen Center for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Norway TOP Study, Building 49, Oslo University Hospital, Ullevål, Kirkeveien 166, PO Box 4956 Nydalen, 0424, Oslo, Norway Full list of author information is available at the end of the article

diagnosed BD has a negative impact on the course of illness. Since these two studies are based on hospitalized patients in two university hospitals with well-acknowledged BD research groups, their patient samples might be biased towards patients with a higher severity of illness.

The current study is based on patients recruited during their first adequate treatment for a manic episode from both inpatient and outpatient services in a catchment area based treatment system, and subsequently followed up after one year. We here aim to ascertain the rate of continued cannabis use over the first year of treatment in patients with recent onset BD and identify clinical outcomes associated with continued use, by exploring the relationship between cannabis use patterns over the follow-up period and clinical status at one year follow-up.

Methods

One hundred and one patients with recent onset DSM-IV [23] BD-I were recruited consecutively from 2003 until 2013 from in- and outpatient units at all major hospitals in the Oslo area as a part of The Thematically Organized Psychosis (TOP) Study at the University of Oslo and Oslo University Hospital. The patients had both psychotic and non-psychotic forms of bipolar disorder. Out of these, 62 patients (63%) participated in a personal follow-up examination after one year. Of the 39 patients that did not attend the follow-up, 20 had decided to withdraw from the study, 18 had moved and were impossible to reach and one patient had died. There were no significant differences in baseline demographic and clinical characteristics between follow-up participants and study drop-outs.

The full inclusion criteria were as follows: meeting DSM-IV diagnostic criteria for BD I, being within the first year of receiving adequate treatment for a manic episode, age between 17 – 65 years. Patients were excluded from the study if they had pronounced cognitive deficits (IQ lower than 70), a neurological disorder, moderate/severe head injury, or were not able to speak a Scandinavian language or to give written informed consent. The patients were given both oral and written descriptions of the study before consenting to participate. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Assessments

Patients referred to the study were interviewed by trained research fellows (psychologists and medical doctors). Diagnosis and episodes of illness were determined at baseline using the Structural Clinical Interview for DSM-IV Axis I disorders (SCID module I, chapters A-E) [24], with the aid of medical charts. For more details, see

[1]. Patients were interviewed in detail, based on a common semi-structural interview form, about substance use in the six months prior to inclusion and in the follow-up period. Forty-seven patients did not use cannabis at any point during this period, 7 patients used cannabis at baseline but not at follow-up, 2 patients started to use cannabis in the follow-up period while 6 patients used cannabis at both time points. Based on these data, the sample was divided into those with continued cannabis use (defined as any cannabis use at both time points, $n = 6$) and those without continued use (the rest of the patient group, i.e. both non-users and those using at one but not both time-points, $n = 56$). The continued use patients reported an average use of cannabis at both baseline and follow up of 2–3 times a week.

Global functioning was measured using the functioning part of the Global Assessment Functioning scale split version (GAF-F) [25,26]. Cut-off for functional recovery was set at a GAF score of 61 [27]. Current depressive symptoms were assessed with the Inventory of Depressive Symptoms – Clinician rated (IDS-C) [28], current manic symptoms were rated with the Young Mania Rating Scale [29], and current psychotic symptoms were assessed with the positive symptoms subscale of the Positive And Negative Syndrome Scale (PANSS) [30] at both time points.

Medication and socio-demographic data were obtained by clinical interviews supported by medical chart information. Premorbid functioning was measured with the Premorbid Adjustment Scale (PAS), divided into academic and social functioning [31]. Childhood premorbid functioning was chosen due to the young age of the sample. Symptomatic recovery was defined as a lack of affective and psychotic symptoms the previous 6 months (PANSS-P less than 4 and no mood episodes as verified by the SCID).

All clinical personnel completed a training program in diagnostics (SCID) and symptom rating (PANSS), based on the training program at the University of California, Los Angeles. They also attended bi-weekly diagnostic consensus meetings led by experienced clinicians in the field of severe mental illness diagnostics. The inter-rater reliability was good with an overall kappa-score of 0.77 (95% LI [0.60, 0.94]) for diagnoses and ICCs of 0.82 [32] for PANSS positive symptoms and 0.86 for the GAF [1].

Statistical analyses

The statistical package for the social sciences (SPSS) version 20.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. Group comparisons for continuous variables were evaluated with independent sample T-tests, and group comparisons for dichotomous data were evaluated with Chi-squared tests or Fischer's exact tests as appropriate. Level of significance was set to $p < 0.05$,

two-sided. The overall effects of continued cannabis use on key baseline measures and on outcome measures at one-year follow-up were first evaluated with a multivariate analysis of variance (MANOVA) with continued cannabis use as the fixed factor. Outcome dimensions indicated to be different between continued cannabis users and the rest of the patients through the MANOVA, were followed up with a series of hierarchical block-wise multiple linear regressions analyses controlling for possible confounders of this association. In addition to sex and age, variables with strong correlations with both continued use of cannabis and the outcome measure were selected as possible confounders, based on a bivariate analysis. Premorbid academic functioning (PAS) was added to the models in order to investigate the role of premorbid traits in the associations. Hence the baseline measures of YMRS and GAF-F were entered in the first step, age and gender in the second, premorbid functioning in the third step and continued cannabis use in the fourth step of the model. There were no associations between the outcome measures and drug treatment adherence on continued cocaine, amphetamine or alcohol use. These factors were thus not added to the model. Information about patient hospitalisations were not collected, and thus not corrected for. Since global functioning (GAF-F) is highly correlated with mood symptoms, a separate analysis was performed with YMRS at one-year follow up in the second-to-last step. To evaluate the possibility of outliers mediating the main effect, a scatterplot of GAF-F by YMRS scores was performed and examined. Finally, in order to investigate if current cannabis use influenced the results, follow-up analyses were done removing patients with cannabis use at one time-point, but not the other,

from the no continued cannabis use group, thus contrasting the continuous cannabis users from the non-users.

Results

The mean age of the sample was 30.9 years (SD: 9.9 years), and 37 patients (60%) were female. Lifetime cannabis use was reported in 52% of the sample. There were more males in the continued use group ($p < .05$) than in the group without continued use. There were no significant differences in key clinical characteristics at baseline, including YMRS and GAF-F levels. There was a negative association between YMRS and GAF-F, indicating that patients with high levels of elevated mood had poorer functioning. The groups did not differ in any other features (Table 1), including the number in symptomatic remission at follow-up (3 (50%) in the continued cannabis use group vs 38 (68%) in the no continued cannabis use group, $p = .601$). Four (67%) of the patients in the continued cannabis use group had not reached a level of functional recovery compared to 19 (29%) patients in the group without continued use; however, this difference was not statistically significant ($p = .390$).

The MANOVA indicated that the continued use group experienced significantly elevated mood, as measured by the YMRS, and significantly lower global functioning as measured by the GAF-F compared to the group without continued use. The effect size for the difference in GAF-F was high. There were however no significant differences in the levels of depression or psychotic symptoms between the groups (Table 2). Repeating the analyses, this time only contrasting continued cannabis users with non-users, gave the same findings.

The bivariate analysis showed a correlation between continued cannabis use and sex ($-.287$ $p < .05$), and a

Table 1 Demographic and clinical characteristics of patients with- and without continued cannabis use at one year follow-up

	No continued cannabis use			Continued cannabis use			
	N = 56			N = 6			
	N	Mean	SD	N	Mean	SD	p
Age (years)	56	32.3	10.0	6	30.5	9.7	.691
IDS total score	53*	11.2	10.0	6	18.5	11.9	.198
YMRS total score	56	2.3	4.0	6	7.3	5.5	.076
PANSS positive total score	56	8.8	2.6	6	9.7	2.6	.439
GAF-F	56	65.3	16.0	6	49.0	16.1	.056
	N	%		N	%		P
Females	36	64.3		1	16.7		.035
Current use of antipsychotic or mood stabilizing medication	42	79.2		4	66.7		.605

*Missing data.

IDS = Inventory of depression Scale; YMRS = Young Mania Rating Scale; PANSS-P = Positive and Negative Syndrome Scale-Psychotic; GAF-F = Global assessment of functioning.

Table 2 Levels of symptoms and functioning in patients with and without continued cannabis use at one year follow-up (MANOVA between-subject effects)

Measure	No continued cannabis use N = 56		Continued cannabis use N = 6		Mean square	F	P	d
	Mean	SD	Mean	SD				
GAF-F	66.02	15.31	49.00	16.11	1561.12	6.599	.013	1.4
PANSS-P	8.70	2.55	9.67	2.58	5.05	.774	.383	0.9
IDS	11.17	9.89	18.50	11.89	289.60	2.802	.100	0.1
YMRS	2.25	3.90	7.33	5.47	139.53	8.469	.005	-0.3

Wilks' λ 3.299 p = .017

GAF-F = Global assessment of functioning; PANSS-P = Positive and Negative Syndrome Scale-Psychotic; IDS = Inventory of depression Scale; YMRS = Young Mania Rating Scale. Significant values in boldface.

negative correlation between YMRS at baseline and GAF-F at baseline (-.347 p < .01), and between sex and premorbid academic functioning (.357 p < .01). In the regression analysis of elevated mood (Table 3), the initial level of elevated mood contributed significantly and with an even stronger association between elevated mood at follow-up and continued cannabis use than indicated by the bivariate analysis. After controlling for possible confounders of the relationship between global functioning at follow-up and continued cannabis use (Table 4), we found that baseline global functioning and continued cannabis use both contributed significantly in the final model (4A). When correcting for level of elevated mood (YMRS scores) at the second to last step, the impact of continued cannabis use was reduced to a trend level of significance (4B). Gender, age and premorbid functioning (as represented by the childhood level of academic functioning in the presented final model) did not contribute significantly to any of the models. The scatterplot did not indicate any outliers (Figure 1).

Discussion

The main result of the current study is that continued cannabis use had a statistically significant association with elevated mood but not with depressive or psychotic symptoms, over a one year follow-up period in a sample of first treatment BD-I patients. This relationship was not explained by differences in age, gender, premorbid functioning or symptoms at baseline. Continued cannabis use also had a significant association with poorer global functioning, but this association seemed to be mediated by the elevated mood levels.

The finding of an association between continued cannabis use and elevated mood confirms findings from the two existing first-hospitalization samples in addition to several multi-episode samples [2,6,14,19,20,22,33,34] and supports the hypothesis that cannabis use in these groups is particularly associated with a higher risk for elevated mood [3-6]. The association was not fully explained by baseline levels of mood symptoms. Furthermore, premorbid functioning did not contribute to the explanation, contrary to findings in schizophrenia [35,36].

Table 3 Multiple regression analysis with elevated mood (YMRS scores) at 1 year as dependent variable

Block no. variable	Block model summary for each step		Contribution of separate variables for last step				
	R2 change	F change	Beta	t	P Value	95% CI of B	
						Lower	Upper
Constant		2.630	.011	.423	3.111
1	.098	6.526					
YMRS (Baseline)			.313	2.555	.013	.047	.389
2	.024	.791					
Sex			-.076	-.604	.548	-2.886	1.547
Age			-.152	-1.201	.235	-.179	.045
3	.042	2.862					
Premorbid childhood academic functioning			.212	-1.629	.096	-.140	1.664
4	.115	8.913					
Continued use of cannabis			.360	2.985	.004	1.729	8.781

Total model: F 4.329 p = .002. Adj r² .214.

Table 4 Multiple regression analysis with GAF-F at one year follow-up as dependent variable

Block no. variable	Block model summary for each step		Contribution of separate variables for last step				
	R2 change	F change	Beta	t	P Value	95% CI of B	
						Lower	Upper
Constant		4.432	.000	22.543	59.633
1	.095	6.270					
GAF-F (Baseline)			.308	2.504	.015	.087	.779
2	.024	.780					
Sex			-.158	-1.247	.217	-13.794	3.202
Age			-.020	-.162	.872	-.461	.392
3	.028	1.895					
Premorbid childhood academic functioning			-.178	-1.377	.174	5.997	1.110
Model A							
4	.119	9.052					
Continued use of cannabis			-.363	-3.009	.004	-33.745	-6.770
Model B							
4	.277	26.934					
YMRS (at 1 yr)			-.565	-.5190	.000	-2.991	-1.325
5	.032	3.224					
Continued use of cannabis			-.200	-1.796	.078	-23.582	1.293

Total model: A F 4.047 p = .003. Adj r² .200.
 Total model: B F 7.675 p = .000. Adj r² .456.

The finding of worse global functioning in the continued cannabis group is in line with previous studies of multi-episode inpatients with BD [20,33] and negative effects of continued cannabis use in general in BD [37,38]. Our findings indicate that the reduction in global function is partly mediated by elevated mood. The lack of an association between continued cannabis use and depression is in line with a recent systematic review

and meta-analysis of mainly multi-episode samples [39]. The lack of an association with psychotic features is slightly surprising given the extensive amount of studies on the relationship between cannabis and psychosis risk [40-43], but we cannot rule out a type II error due the low number of continued cannabis users, and this finding warrants further research. The YMRS contains items of psychotic manic symptoms [29]. The lack of an association between continued cannabis use and psychotic features could strengthen the notion of a primary association to mood symptoms since this indicates that the higher YMRS scores are not mainly based on psychosis-related items [29], a view supported by the findings of an association between poorer global functioning and elevated mood also at baseline. The effect of continued cannabis use on outcome measures after 12 months did not seem to be explained by premorbid traits, further strengthening a hypothesis of a direct association between cannabis use and outcome.

Strengths and limitations

The main strength of the study is the well characterized and relatively large prospective sample of patients followed during one year after the first treatment for mania in BD-I. The catchment area based consecutive sampling procedure including both in-and outpatient treatments services gives the sample a high degree of representativity.

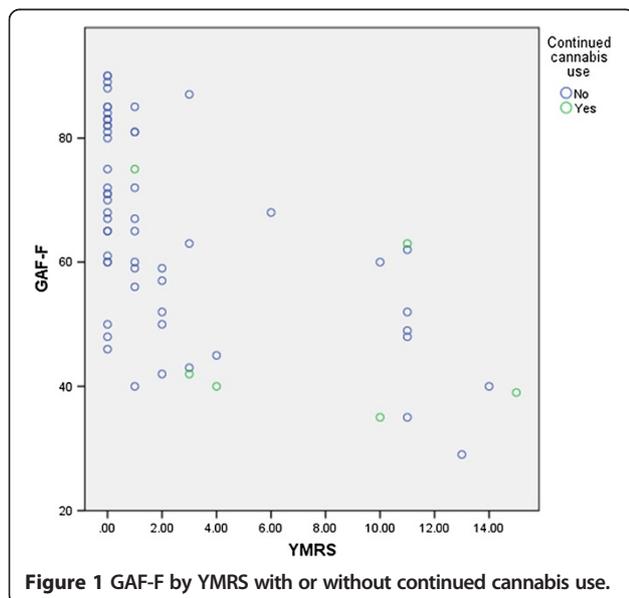


Figure 1 GAF-F by YMRS with or without continued cannabis use.

The low number of continued use patients is our main limitation, but is unlikely to induce type I errors since results did not appear to be driven by outliers. However, type II errors cannot be ruled out. This is a longitudinal study with two cross-sectional points of assessment; we thus lack reliable data of temporal sequencing of cannabis use and mood symptoms in the follow up period. It is thus not possible to conclude with certainty which phenomenon that drives the other. Information about cannabis use was based on self-reports. Self-reports of substance use have however been shown to have considerable validity in earlier studies [44–46].

Conclusion

In conclusion, the current study showed that patients with continued cannabis use throughout the first year of treatment of BD I were at higher risk for elevated mood and worse global functioning compared to the patients without continued cannabis use. The poorer functioning seemed to be, at least in part, mediated by the elevated mood. These findings indicate that continued cannabis use, also below the threshold for a DSM-IV diagnosis of abuse or dependency, may have important clinical implications for patients suffering from BD-I. Future research should aim at replicate these findings in a larger sample to minimize the risk of type II errors.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LRK collected data and carried out analyses and interpretation of the data and drafted the manuscript. IM and PAR designed and planned the study, collected data, analysed and interpreted the data, and revised the manuscript critically. SRA, CD and TVL all collected data and helped revise the manuscript critically. OAA designed and planned the study, collected data and revised the manuscript critically. All authors read and approved the final manuscript.

Acknowledgements

Norwegian research council grant 181831, NASATS grant 217776, NORMENT grant 223273, South-Eastern Norway Regional Health Authority grants 2007069, 2011033, 2011085.

Author details

¹NORMENT, KG Jebsen Center for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Norway TOP Study, Building 49, Oslo University Hospital, Ullevål, Kirkeveien 166, PO Box 4956 Nydalen, 0424, Oslo, Norway.

²Division of Mental Health Services, Department of Specialized Inpatient Treatment, Akershus University Hospital, Akershus, Norway. ³Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway.

Received: 1 September 2014 Accepted: 15 January 2015

Published online: 05 February 2015

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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

The authors state that this work is their own and has not been submitted for publication elsewhere. This work is supported by a research agreement from GW Pharmaceuticals.

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.

ACKNOWLEDGEMENTS

The authors acknowledge the contributions of the patients who responded to this questionnaire and of the software team who developed and administered the database.

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Paper received March 2004, accepted May 2004

MARIJUANA BASELINE HEALTH STUDY

FINAL REPORT | JULY 2019



MASSACHUSETTS DEPARTMENT
OF PUBLIC HEALTH
250 WASHINGTON STREET
BOSTON, MA 02108

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Suggested Citation:

Massachusetts Department of Public Health (2019). *Marijuana Baseline Health Study*. Retrieved from <https://www.mass.gov/report/massachusetts-department-of-public-health-marijuana-research>

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Massachusetts Department of Public Health
250 Washington Street
Boston, MA 02108
617.624.6000
www.mass.gov/dph

Table of Contents

Executive Summary	4
Acknowledgements	6
Introduction	8
Task 1: Prevalence and Perceptions of Marijuana Use	15
Chapter 1: Retrospective Analysis of Indicators of Use and Perceptions of Marijuana..	15
Chapter 2: Prevalence and Correlates of Marijuana Use among Adults in Massachusetts	31
Chapter 3: Use and Perceptions of Marijuana among Adult Medical Use of Marijuana Patients in Massachusetts	52
Task 2: Incidents of Impairment and Hospitalization	151
Chapter 1: Measuring Marijuana Exposure and its Effects Related to Driving Impairment: A State of the Science Review	151
Chapter 2: Driving Under the Influence of Marijuana and Marijuana-Involved Motor Vehicle Crashes in Massachusetts	183
Chapter 3: Marijuana-Related Health System Contacts in Massachusetts.....	219
Task 3: Economic and Fiscal Impacts	235
Chapter 1: From Medical to Retail Marijuana: Estimating Fiscal Effects of Legalization In Massachusetts	235
Appendix	269
Appendix A DPH Statewide Survey Tool	270
Appendix B DPH Patient Survey Tool	275
Appendix C Economic and Fiscal Model Inputs.....	305
Table C.1. Model Inputs and Data Sources.....	306
Figure C.1. New Revenue or Savings Estimated Post-Legalization, by Source.....	309
Figure C.2. Estimated Two-Year Local Tax Revenue if Registered Marijuana in all Cities/Towns	310
Table C.2. Estimated Two-Year Local Tax Revenue if Registered Marijuana Dispensaries in all Cities/Towns.....	311
Table C.3. Estimated Two Year Local Tax Revenue for each City or Town.....	311
Appendix D Marijuana Product and Price Characterization	318

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).

Acknowledgements

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.

The completion of this study would not have been possible without the assistance of study collaborators from the University of Massachusetts (UMass); Mathematica Policy Research (Mathematica); and JSI Research and Training Institute, Inc. (JSI).

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.

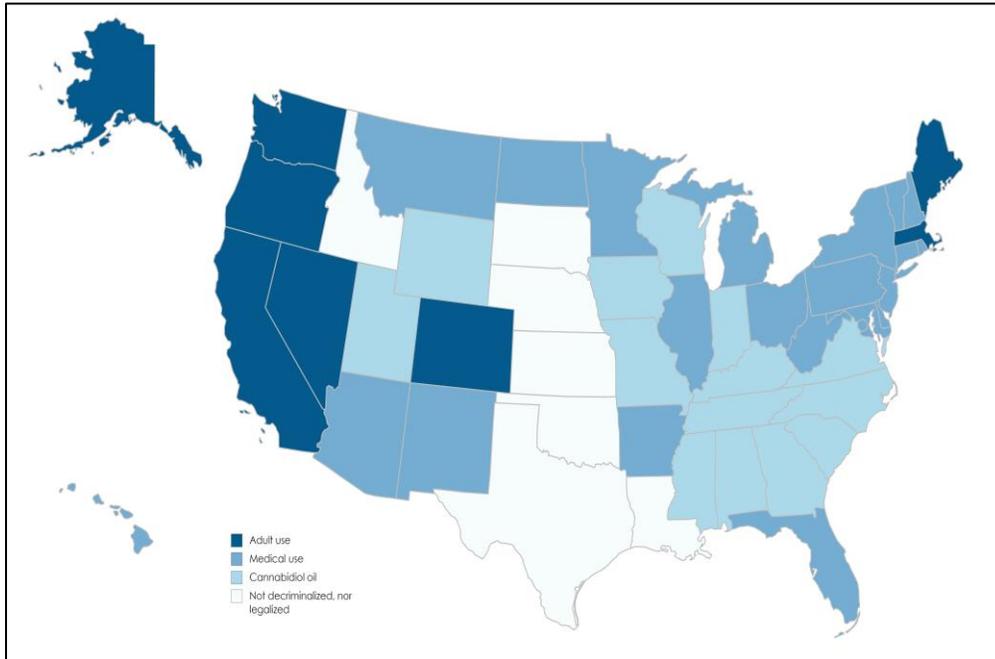


Figure 1: Current marijuana legalization status by state

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.

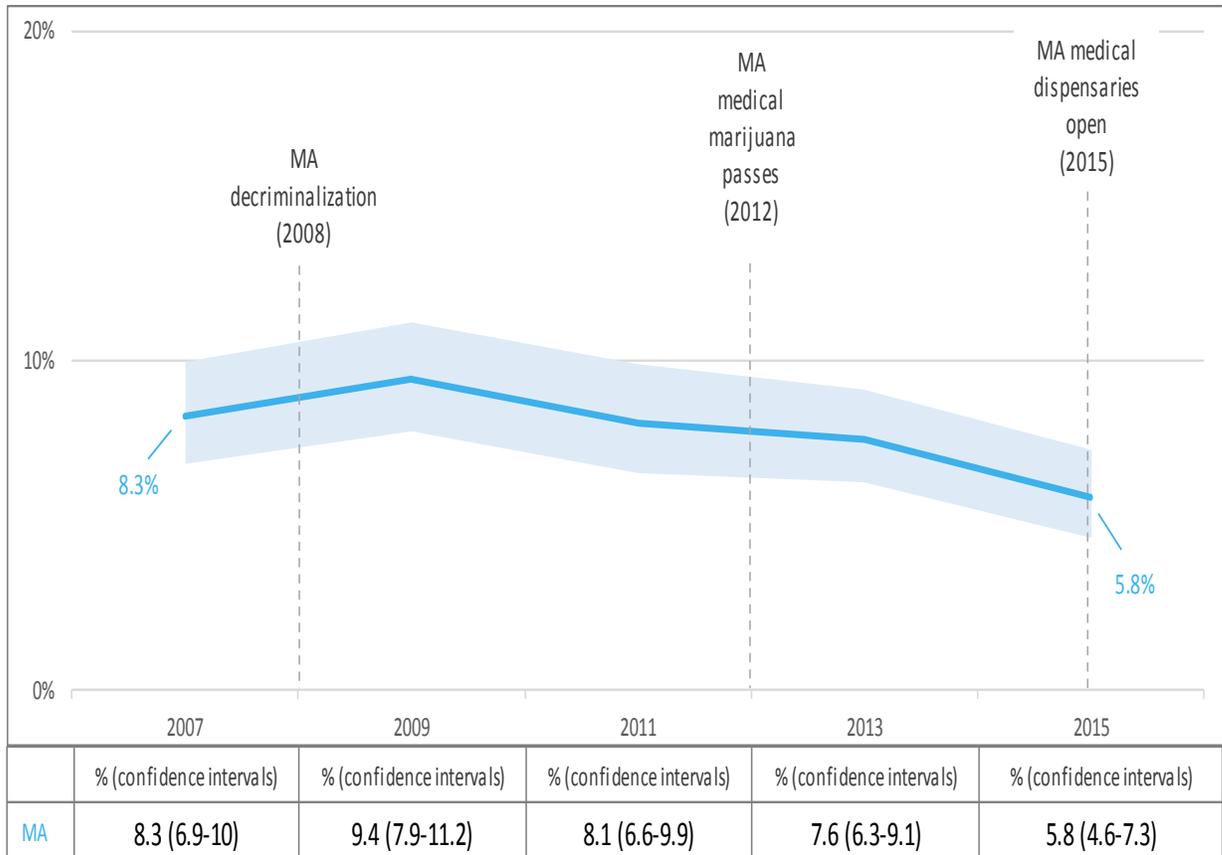


Figure 2: Massachusetts Ever Used Marijuana, Middle School Students

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.

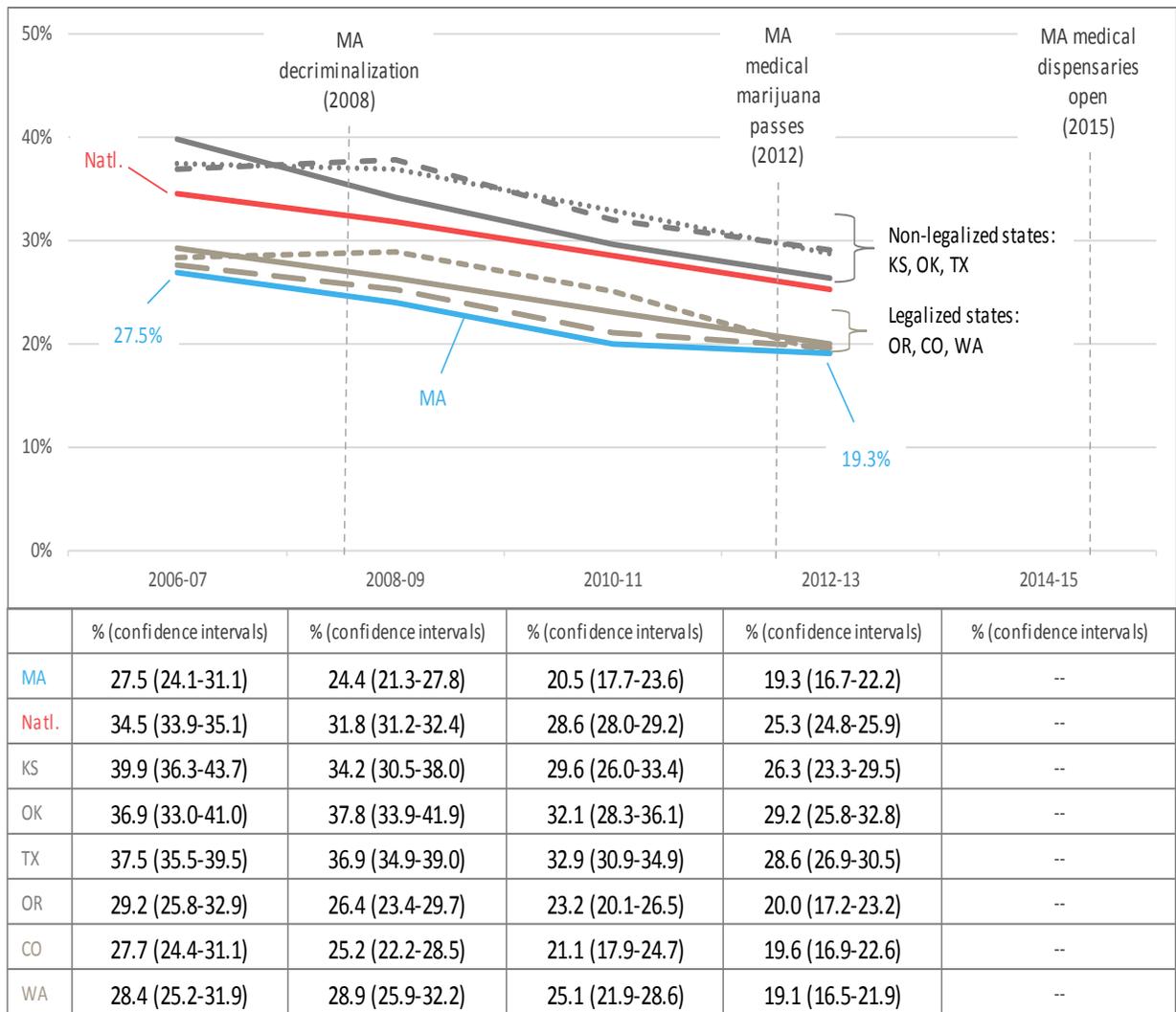


Figure 3: Massachusetts and Comparison States Perceptions of Great Risk of Smoking Marijuana Once a Month, Youth Ages 12-17

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.

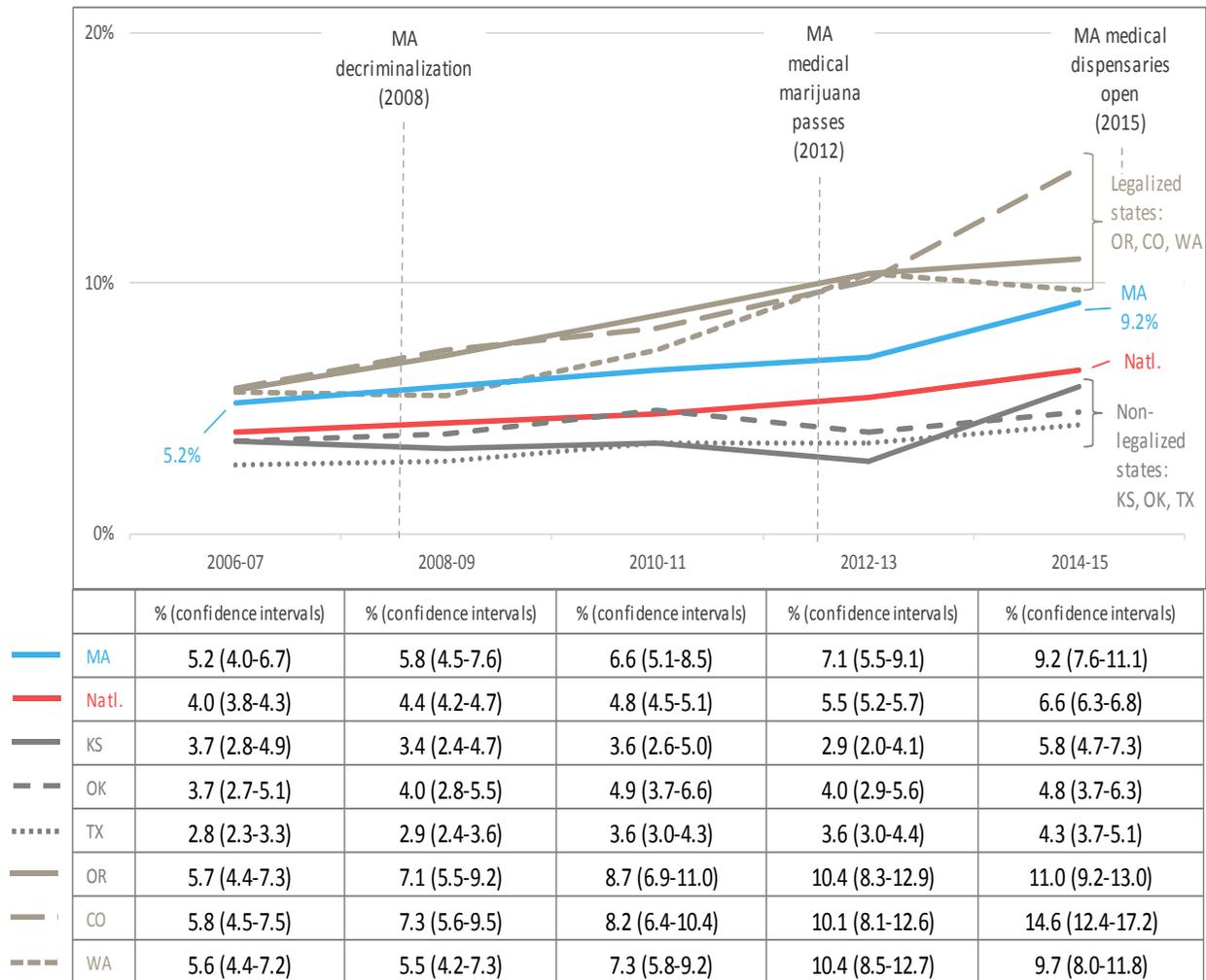


Figure 4: Massachusetts and Comparison States Current Use Ages 26 and Older

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.

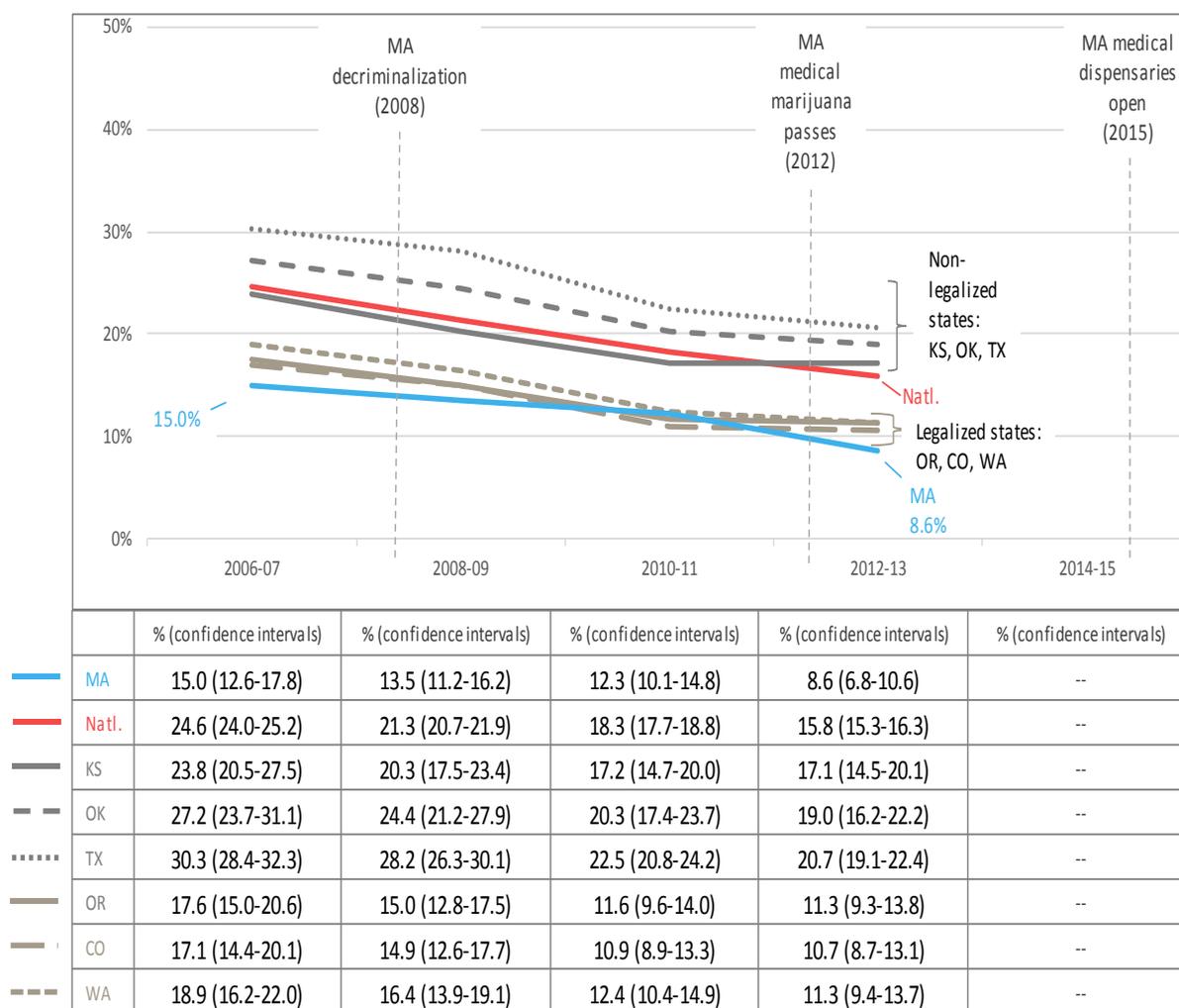


Figure 5. Massachusetts and Comparison States Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 18-25

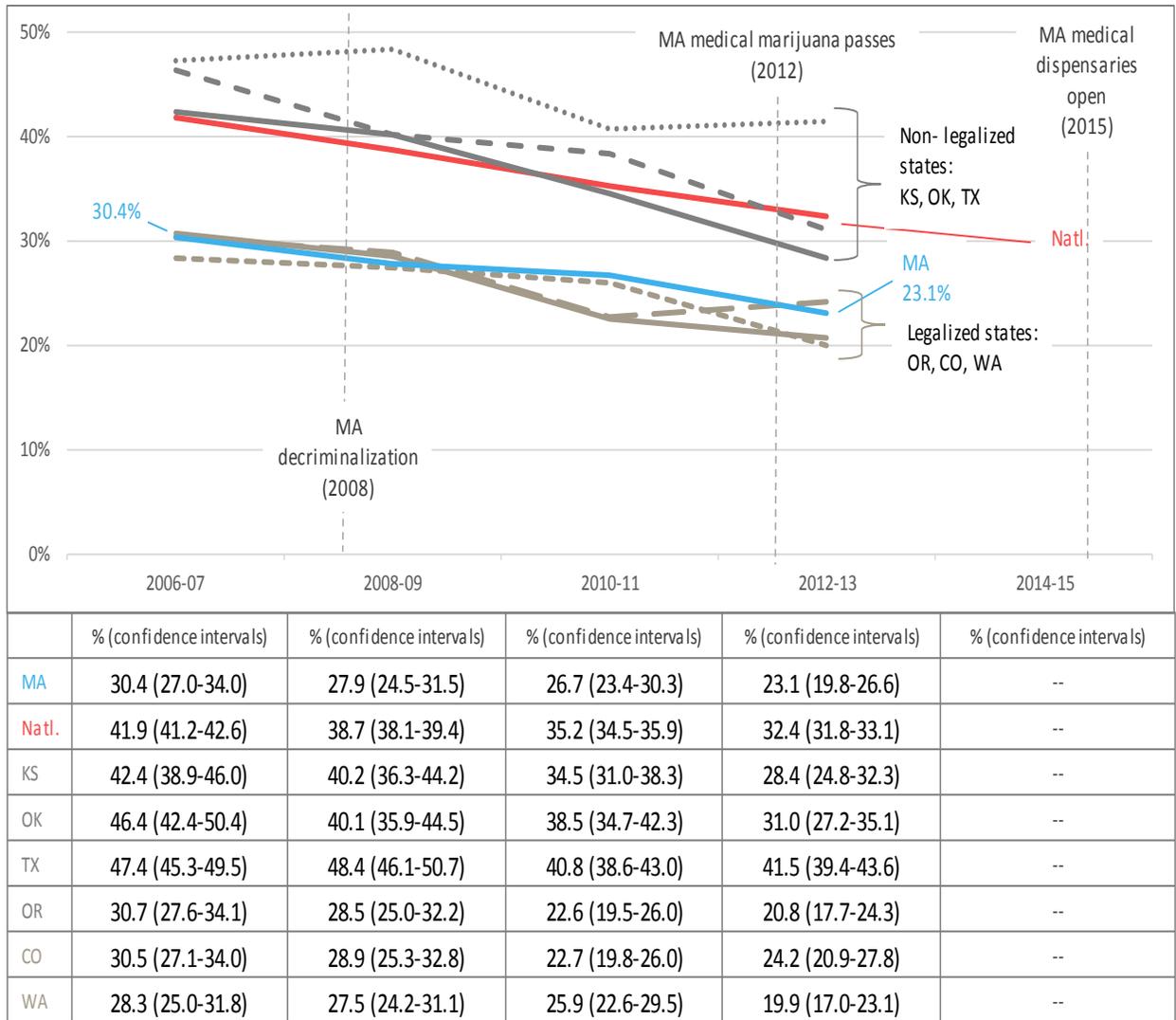


Figure 6: Massachusetts and Comparison States Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 26+

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.

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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.

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**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		
		Male (N=3732)	Female (N=3056)	p-value
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, American Indian or Alaska Native, non- Hispanic	14 0.21	5 0.14	9 0.29	
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		
		≤ 50 years (N=3224)	≥ 51 years (N=2793)	p-value
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	
Treated in emergency room for any reason related to alcohol use	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 device's 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.

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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).

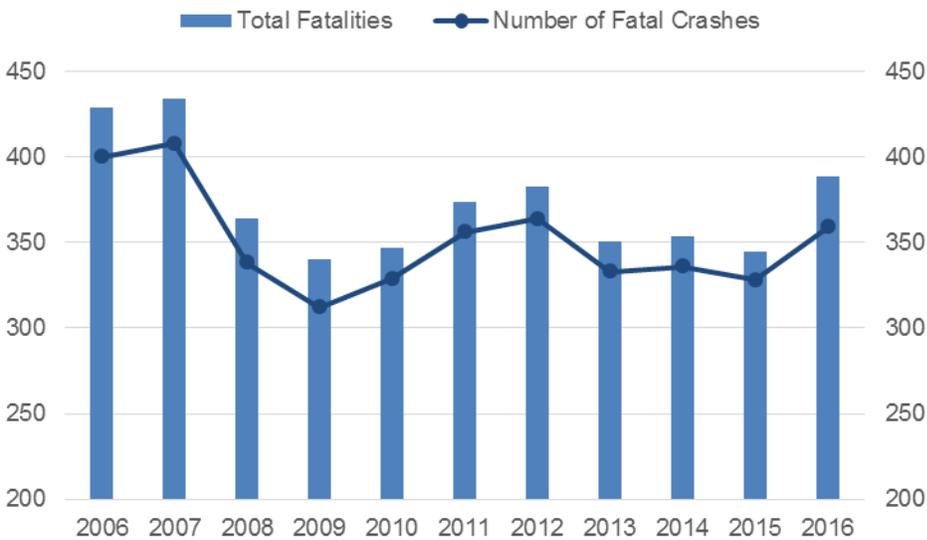


Figure 1. Total fatalities and number of motor vehicle crashes with a fatality in Massachusetts by year (2006-2016)

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.

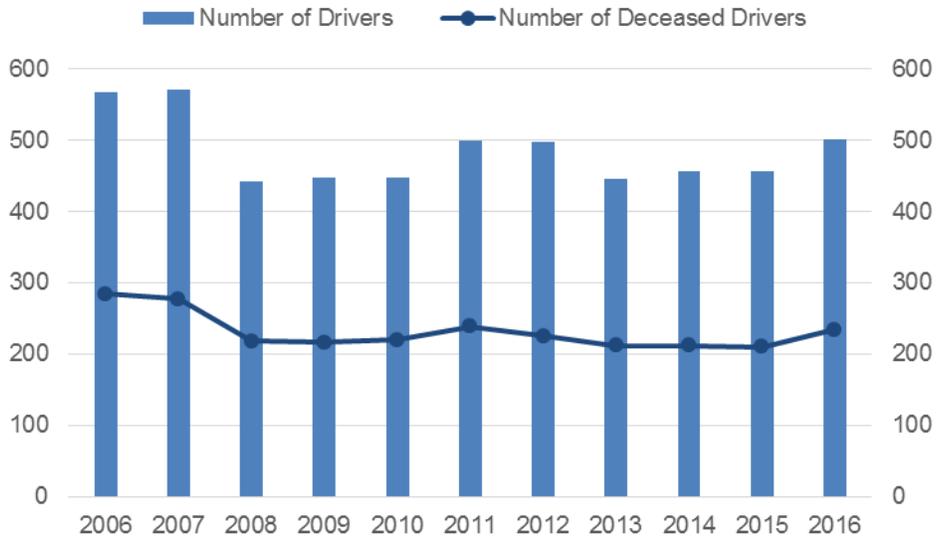


Figure 2. Number of drivers involved in fatal crashes and number of deceased drivers in MA by year (2006-2016)

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.

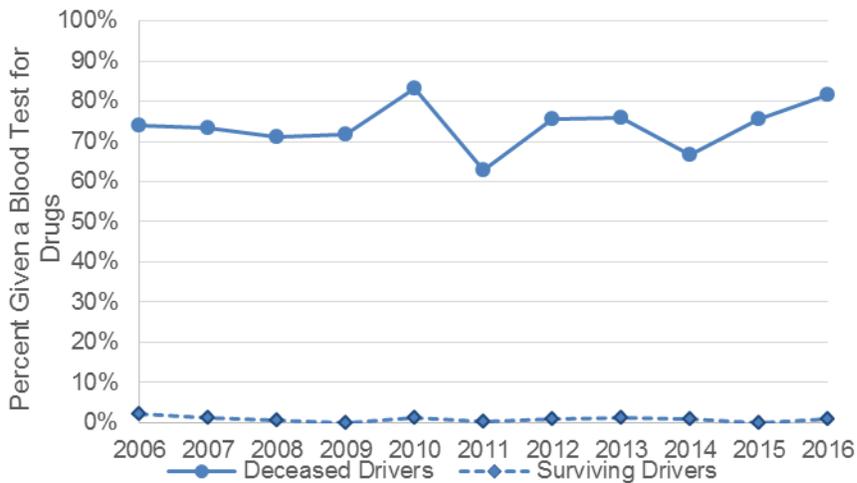


Figure 3. Percentage of deceased and surviving drivers in fatal crashes given a Blood test for drugs

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.”

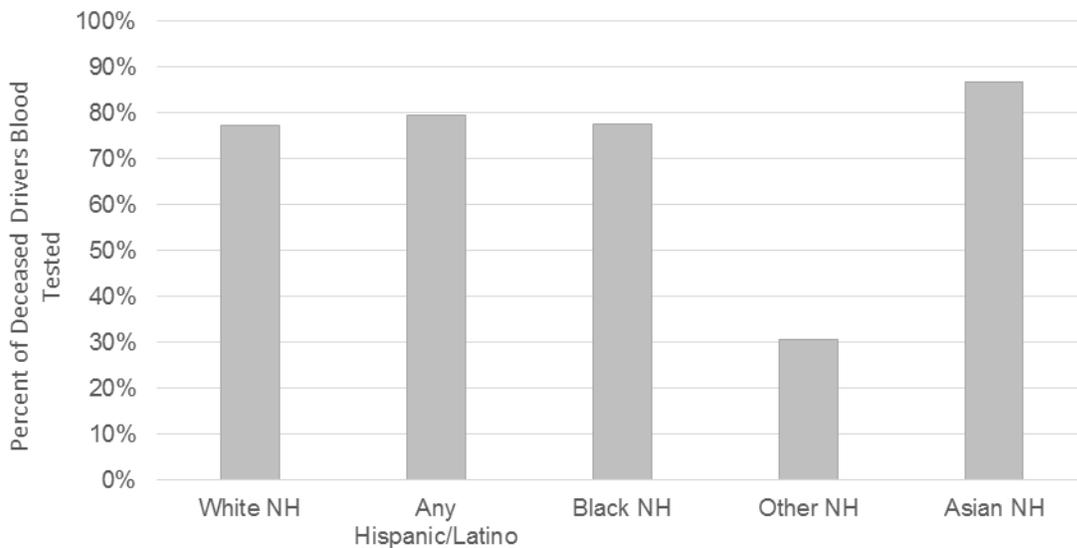


Figure 4. Percent of deceased drivers given a blood test for drugs, by race/ethnicity.

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).

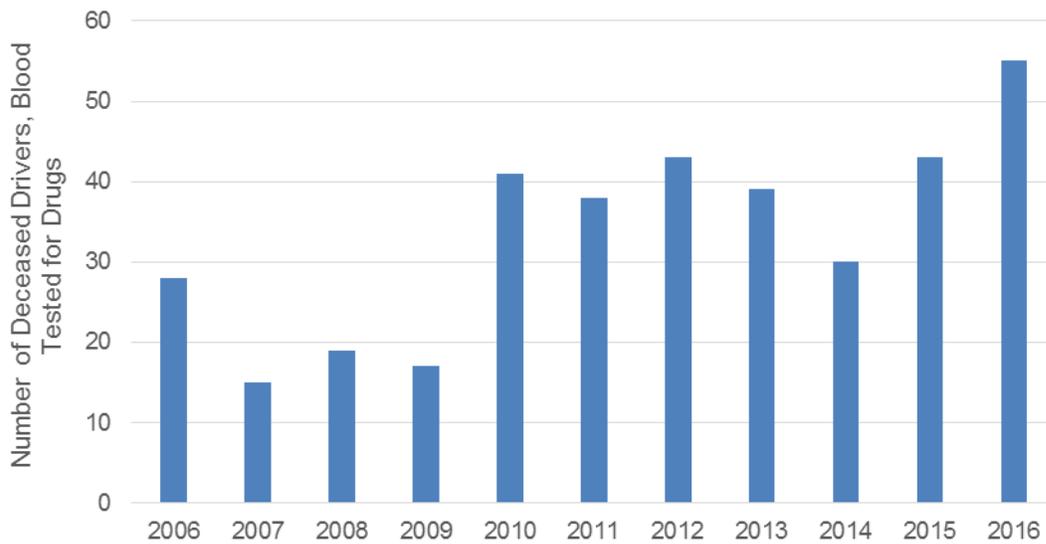


Figure 5. Number of deceased drivers given a blood test for drugs testing positive for any cannabinoid

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).

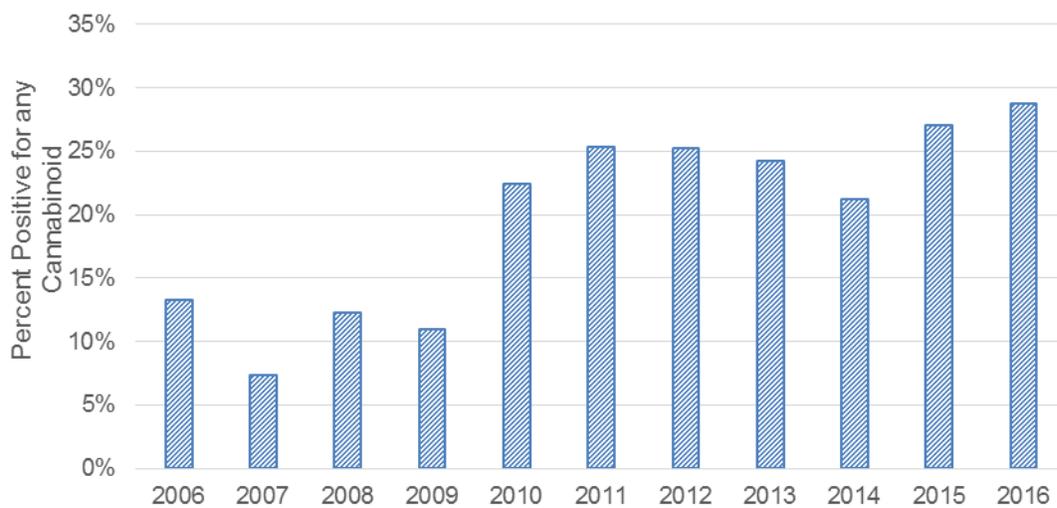


Figure 6. Percentage of deceased drivers given a blood test for drugs who tested positive for any cannabinoid

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).

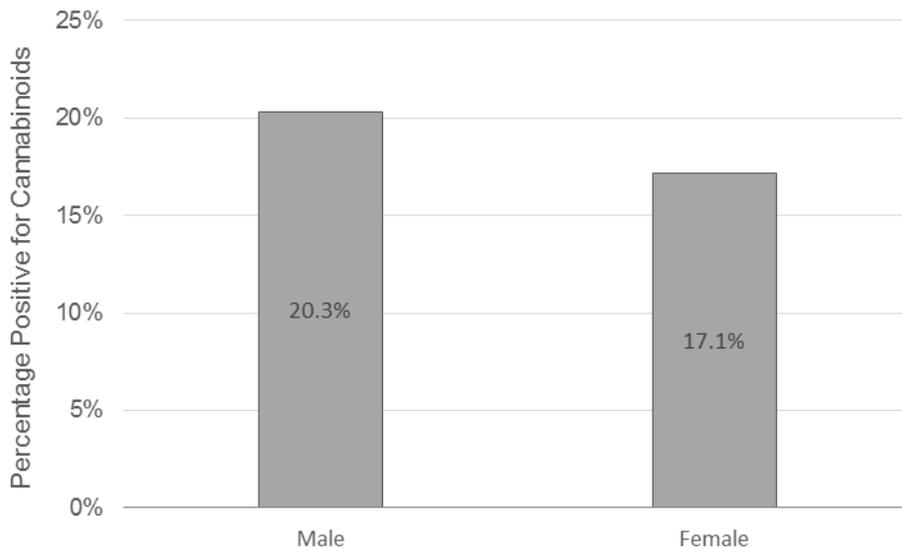


Figure 7. Percentage of deceased drivers given a blood test for drugs who tested positive for any cannabinoid, by driver sex

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.

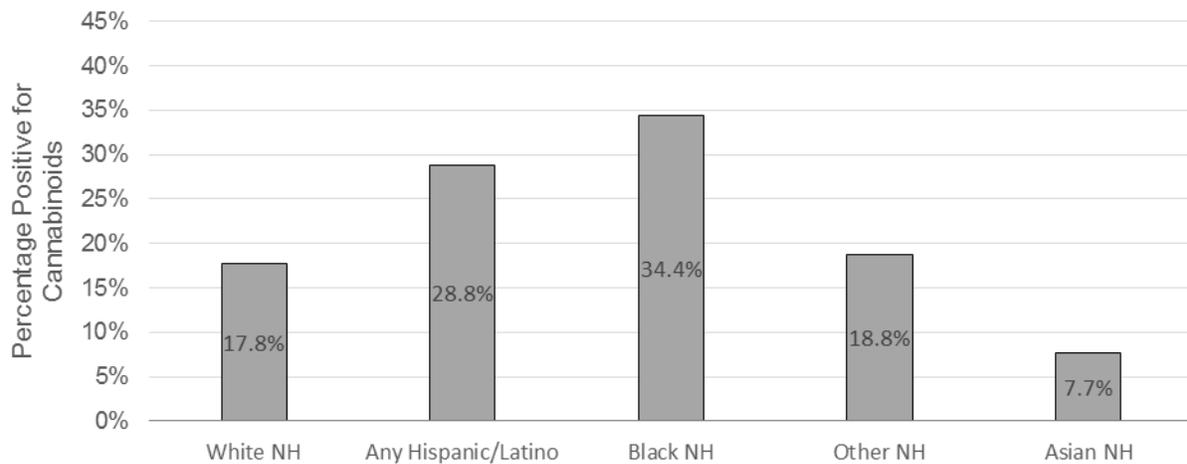


Figure 8. Percentage of all deceased drivers given a blood test for drugs who tested positive for any cannabinoid, by driver race/ethnicity

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.

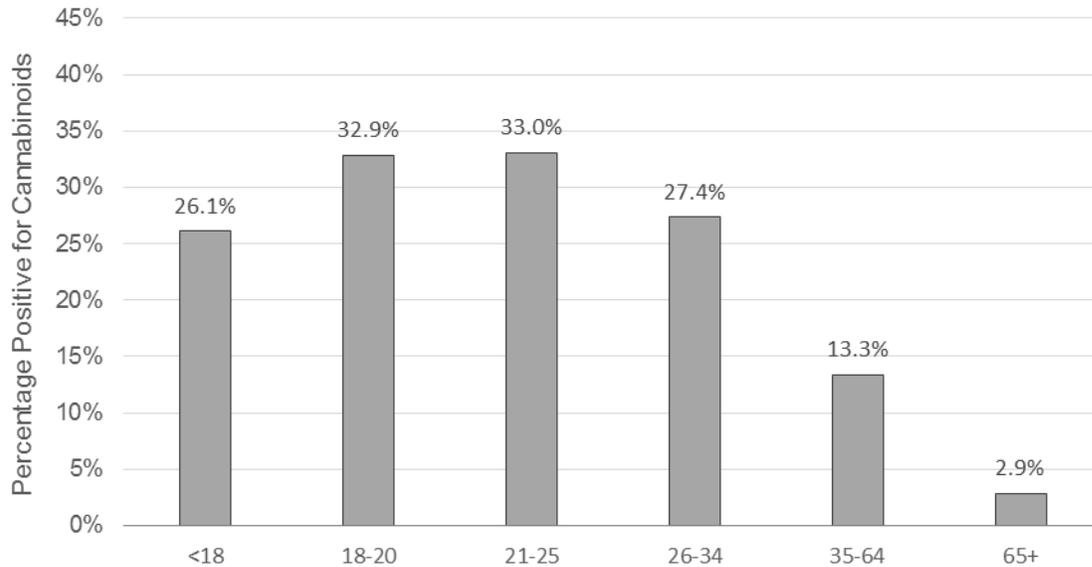


Figure 9. Percentage of deceased drivers given a blood for drugs who tested positive for any cannabinoid by driver age

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.

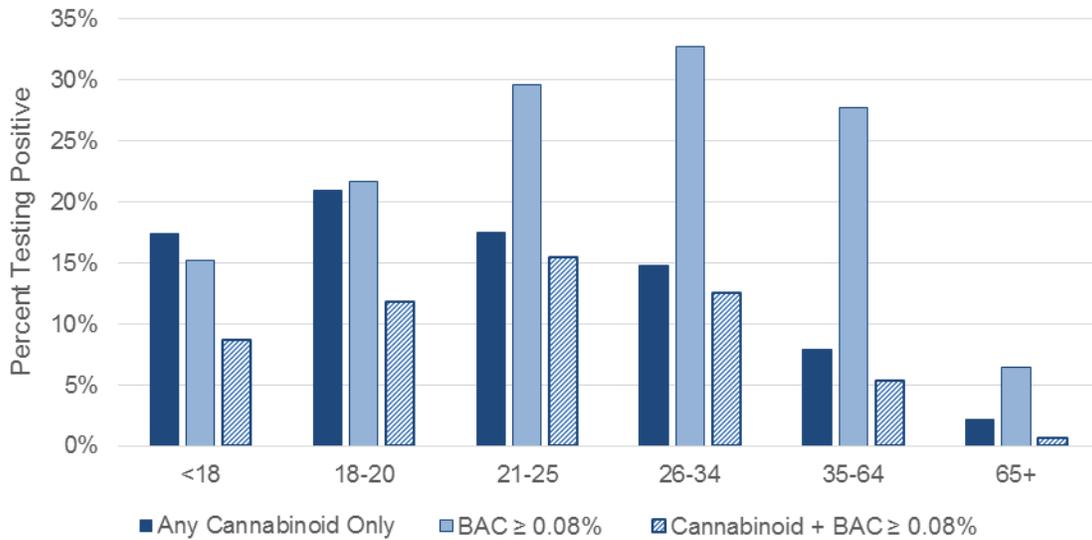


Figure 10. Percentage of all deceased drivers given a blood test for alcohol and drugs who tested positive for any cannabinoid and/or had a blood alcohol content (BAC) ≥ 0.08%, by driver age (years).

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%.

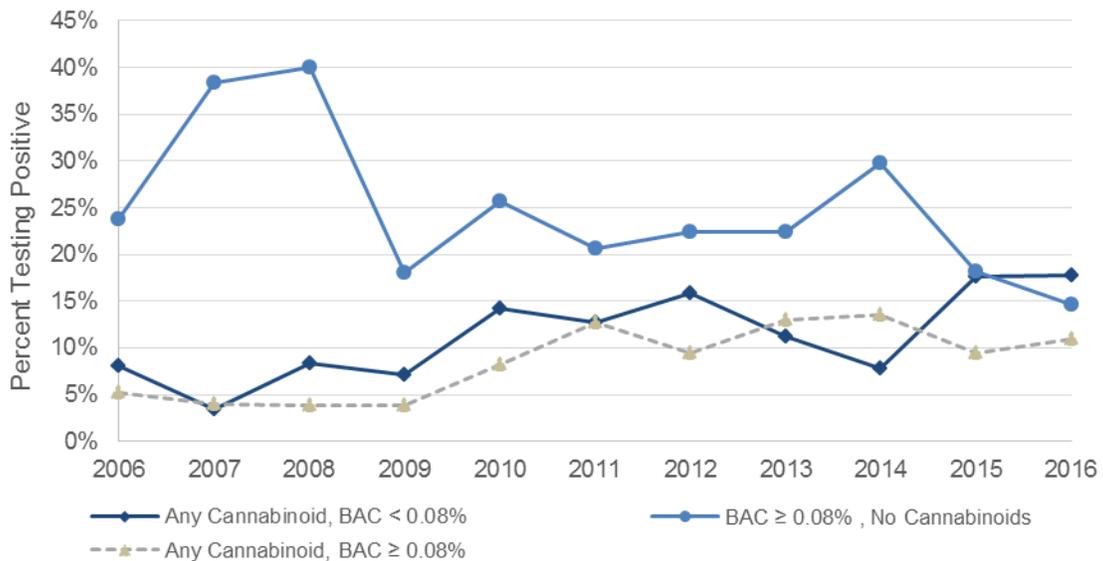


Figure 11. Percentage of all deceased drivers given a blood test for alcohol and drugs who tested positive for any cannabinoid and/or had a BAC ≥ 0.08% in Massachusetts from 2006 to 2016

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.

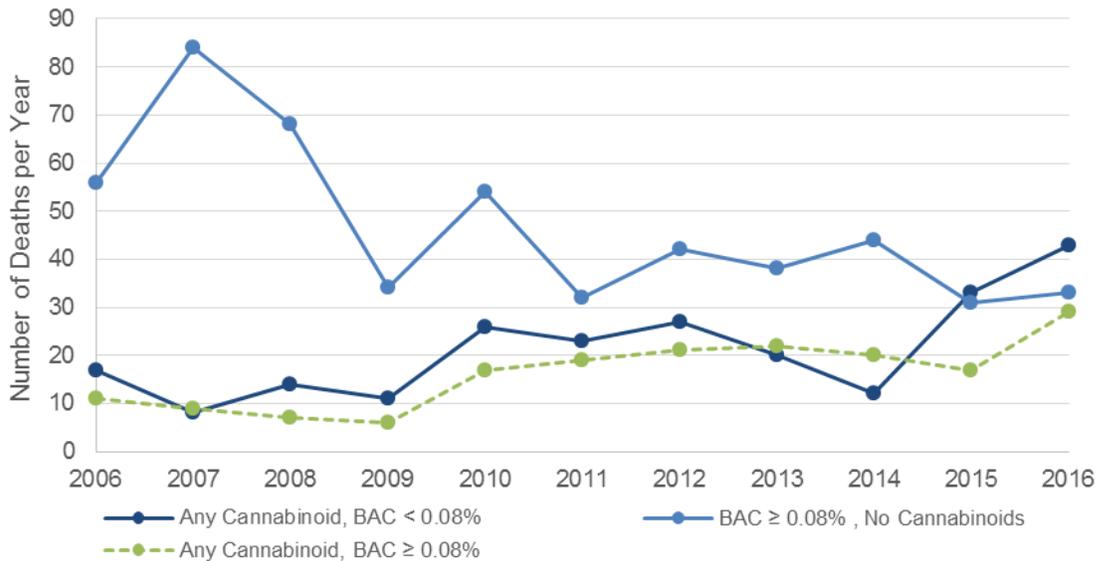


Figure 12. Number of deaths per year resulting from crashes with deceased drivers given a blood test for alcohol and drugs who tested positive for any cannabinoid and/or had a BAC $\geq 0.08\%$ in Massachusetts from 2006 to 2016.

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.

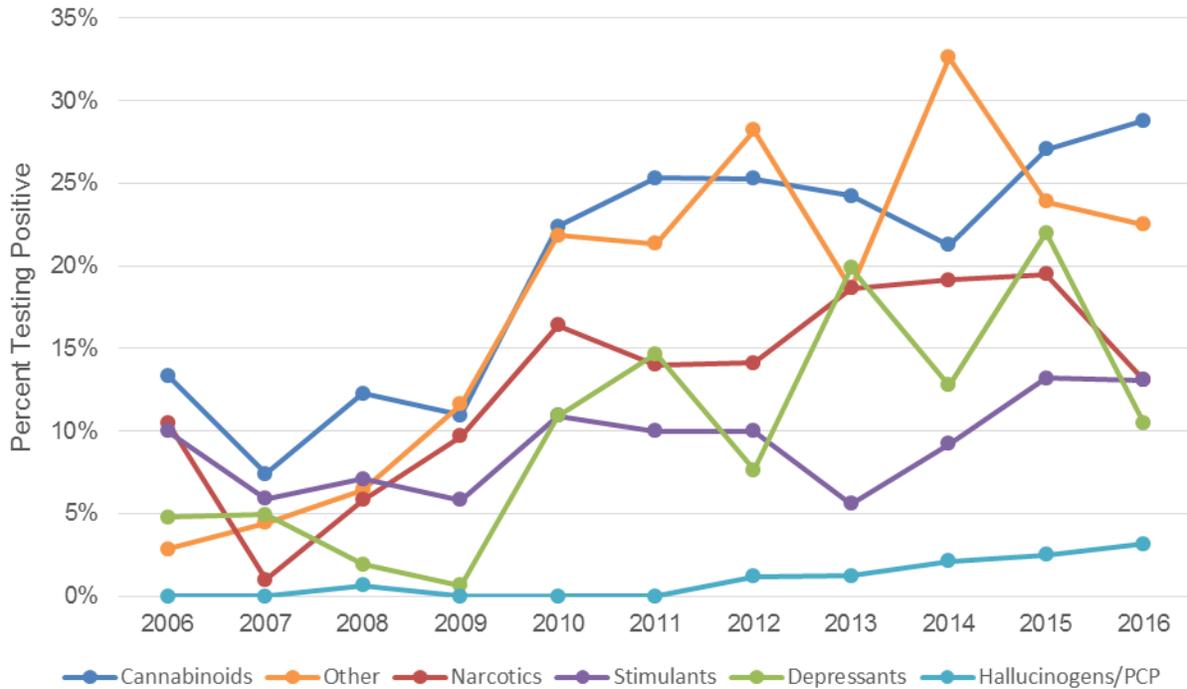


Figure 13. Percentage of all deceased, drivers given a blood test for drugs who tested positive for various drug categories in Massachusetts from 2006 to 2016.

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).

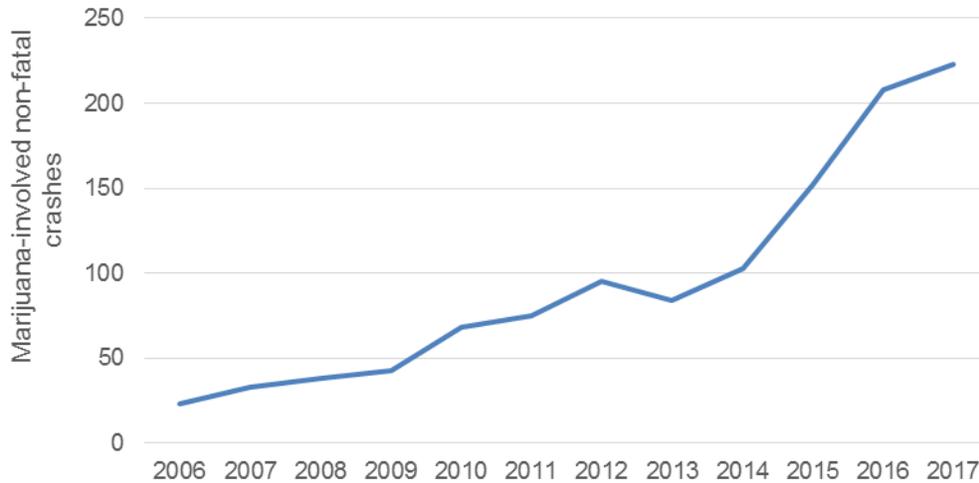


Figure 14. Non-fatal motor vehicle crashes which contain a crash narrative containing the keywords “marijuana”, “weed”, and/or “cannabis,” by year

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.

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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.

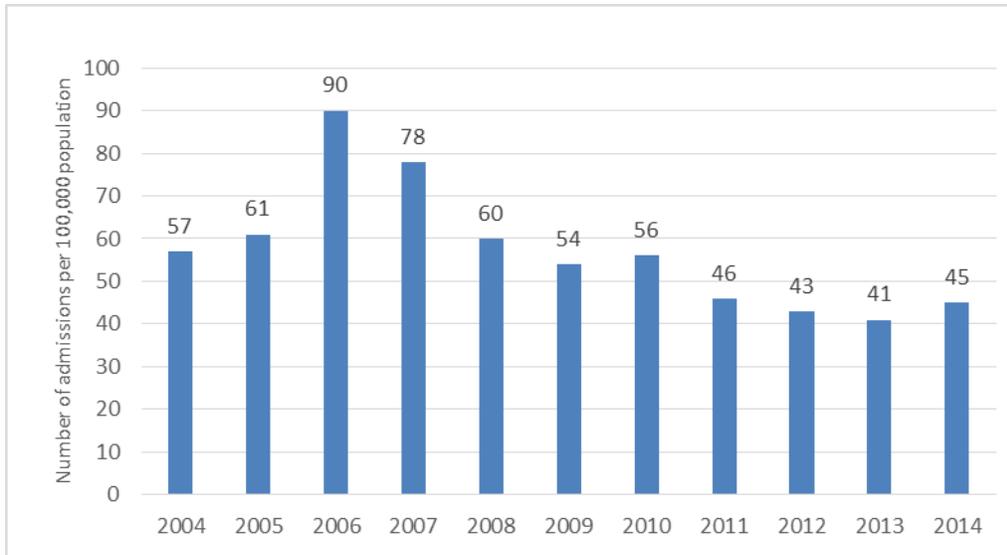


Figure 1. Massachusetts Admissions to Substance Use Treatment with Marijuana as Primary Substance of Abuse, Age 12+, 2004-2014

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.

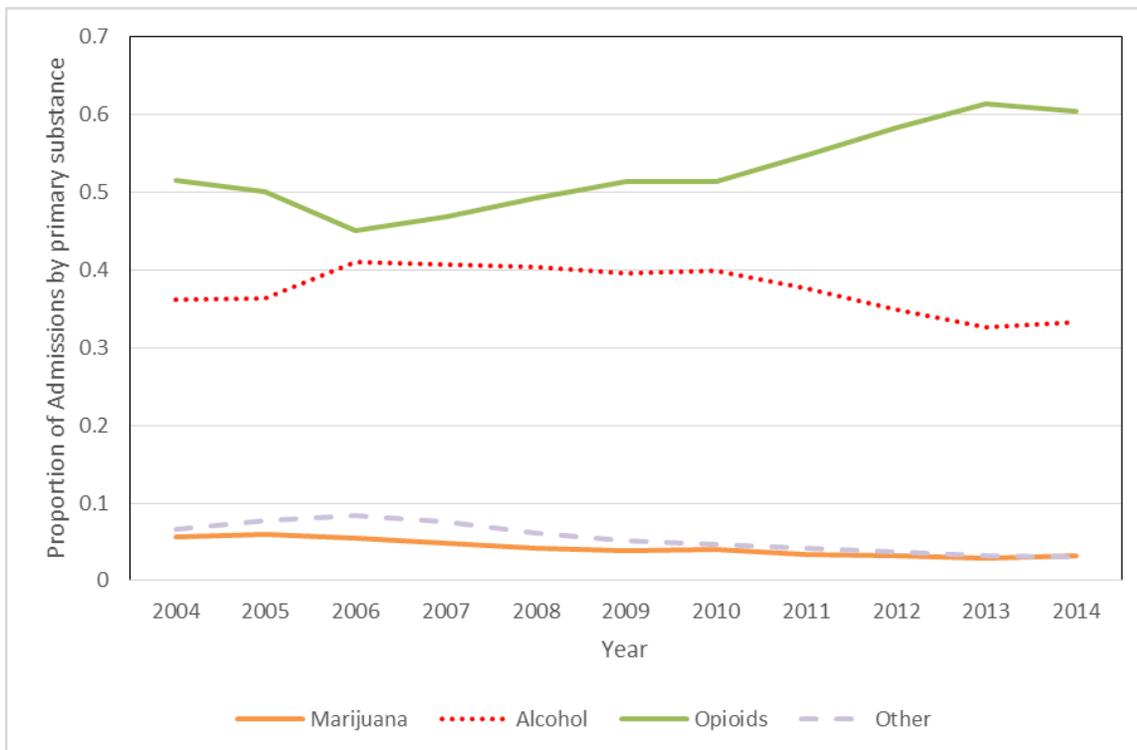


Figure 2. Proportion of Substance Abuse Treatment Admissions by Primary Substance of Abuse, 2004-2014

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).

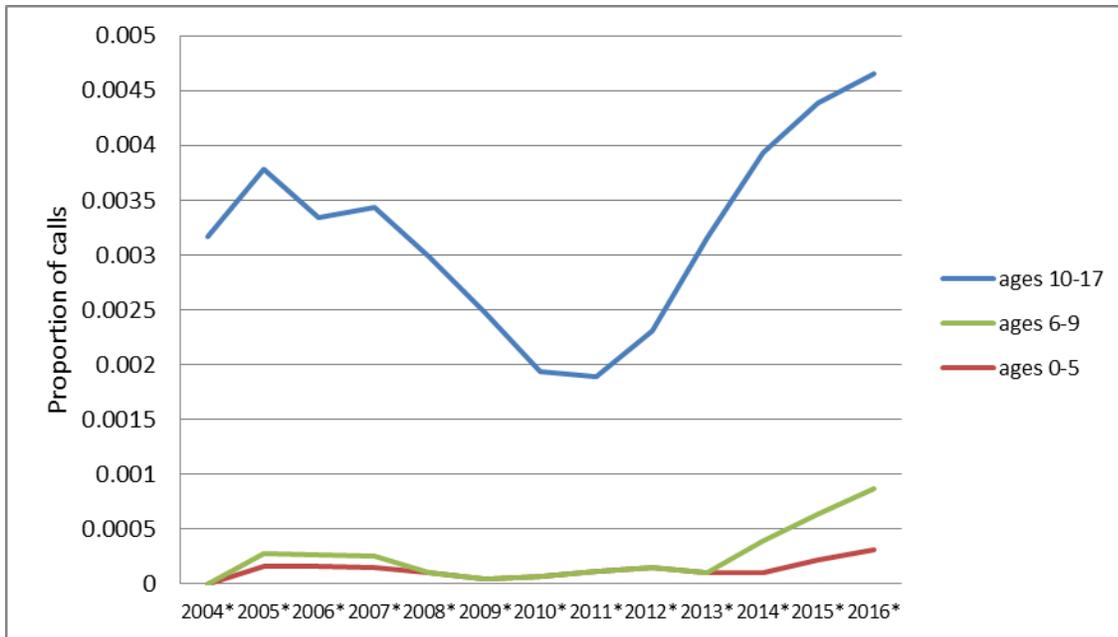


Figure 3. Proportion of MA Poison Control Calls due to Marijuana, Youth Age 0-17, 3-Year Moving Average, and 2004-2016

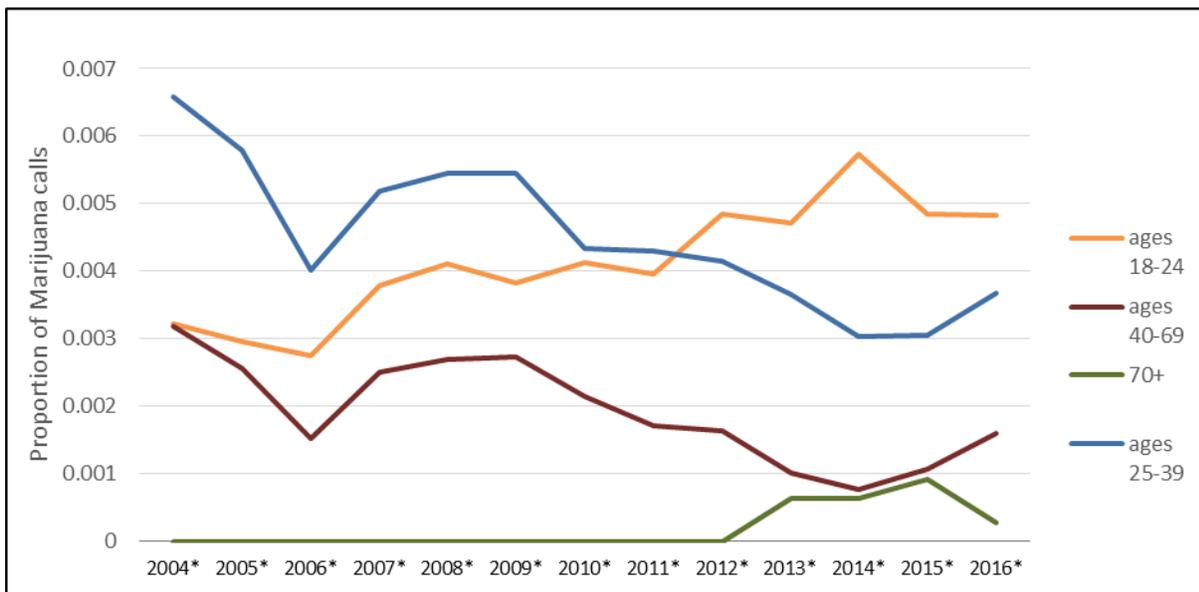


Figure 4. Proportion of MA Poison Control Calls Related to Marijuana Exposure, Adults 18+ Years, 3-Year Moving Average, 2004-2016

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	

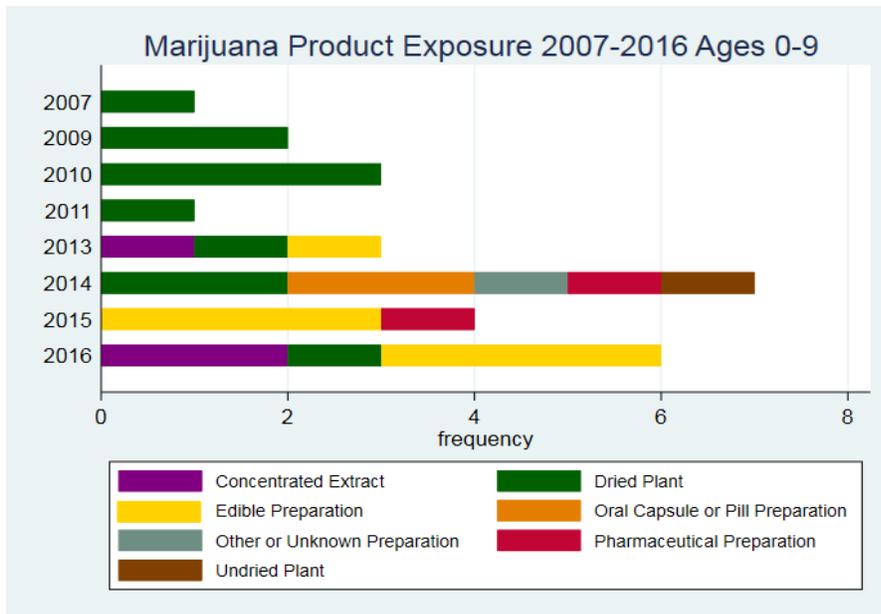


Figure 5. Frequency of Poison Control Center Reported Marijuana Exposures by Product Code, 2007-2016, Age 0-9 Years

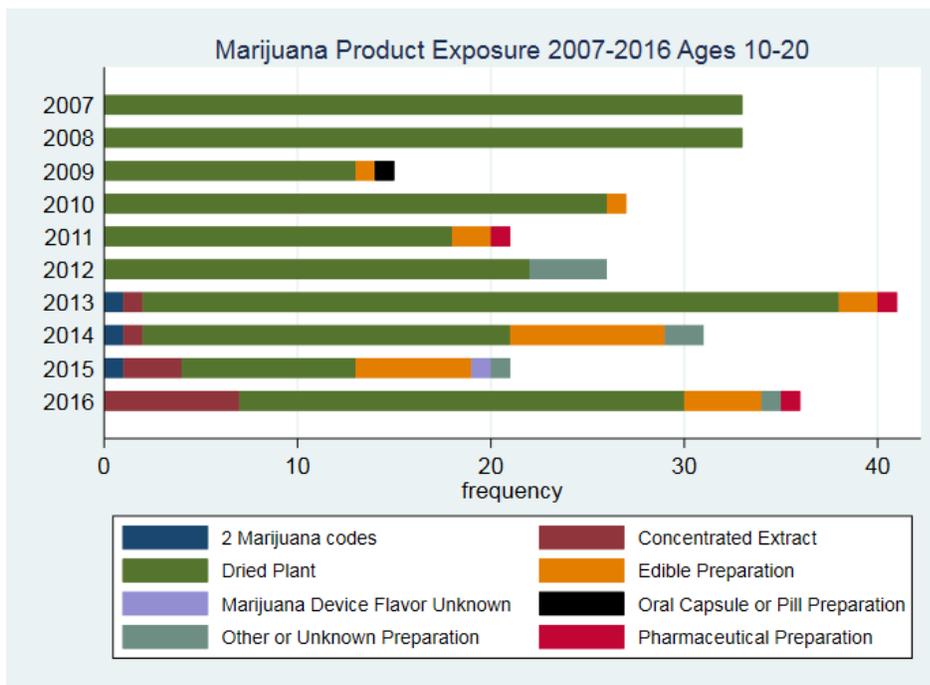


Figure 6. Frequency of Poison Control Center Reported Marijuana Exposures by Product Code, 2007-2016, Age 10-20 Years

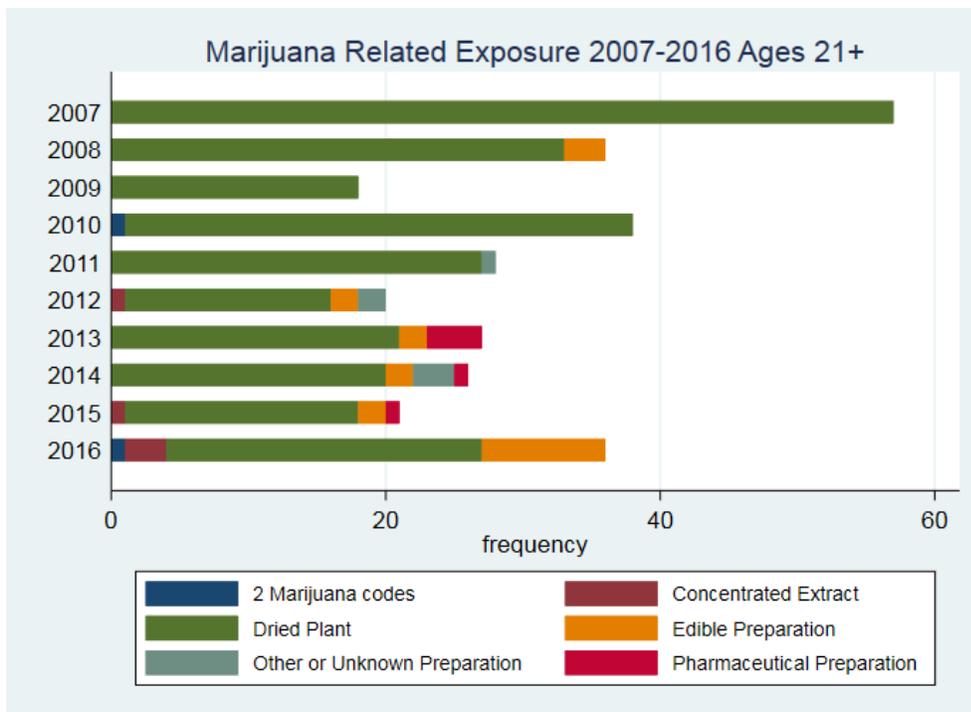


Figure 7. Frequency of Poison Control Center Reported Marijuana Exposures by Product Code, 2007-2016, Age 21 Years and Older

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.

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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).

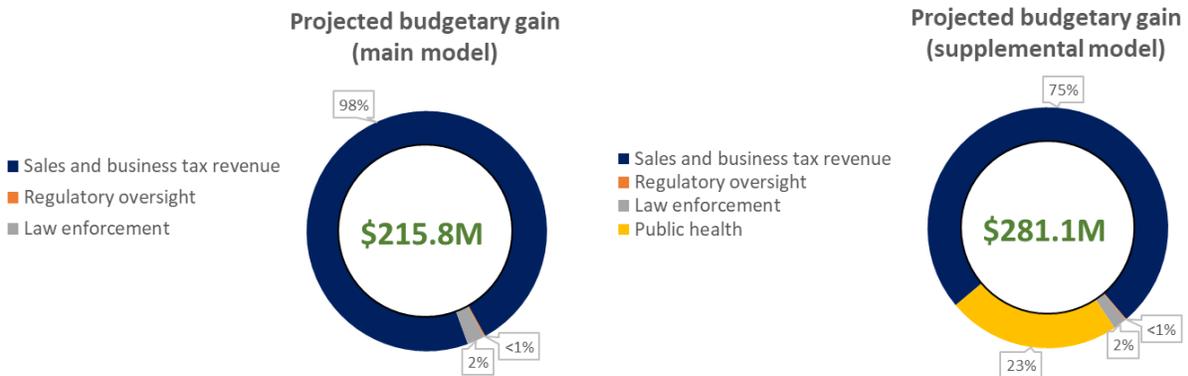
Supplemental Model Impacts

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

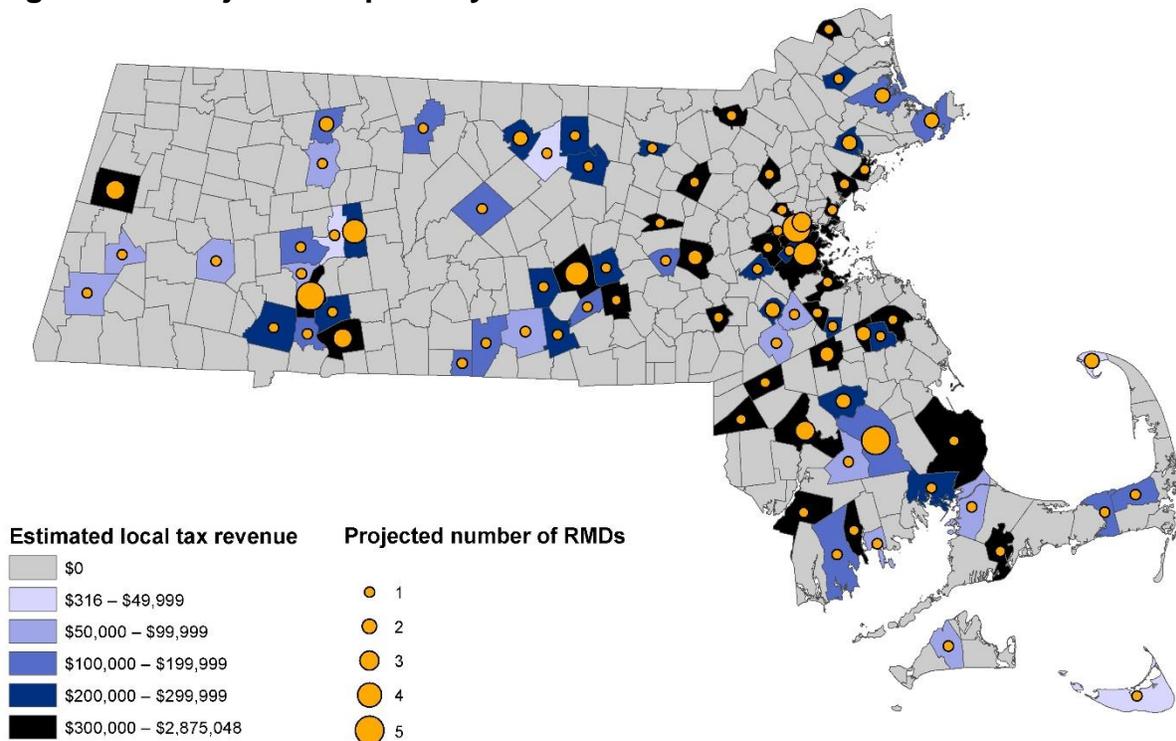
In Figure 2, we show our estimated two-year local tax revenue, assuming a 3% local tax rate, along with information on the projected number of RMDs expected per city or town. With some exceptions, local tax revenue is generally higher on the coast and lower in the western part of the state. In Table 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 spent 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.

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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?

--	--	--	--	--

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):

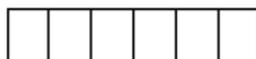
None → Go To Question 34

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] 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 (difficulty 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.

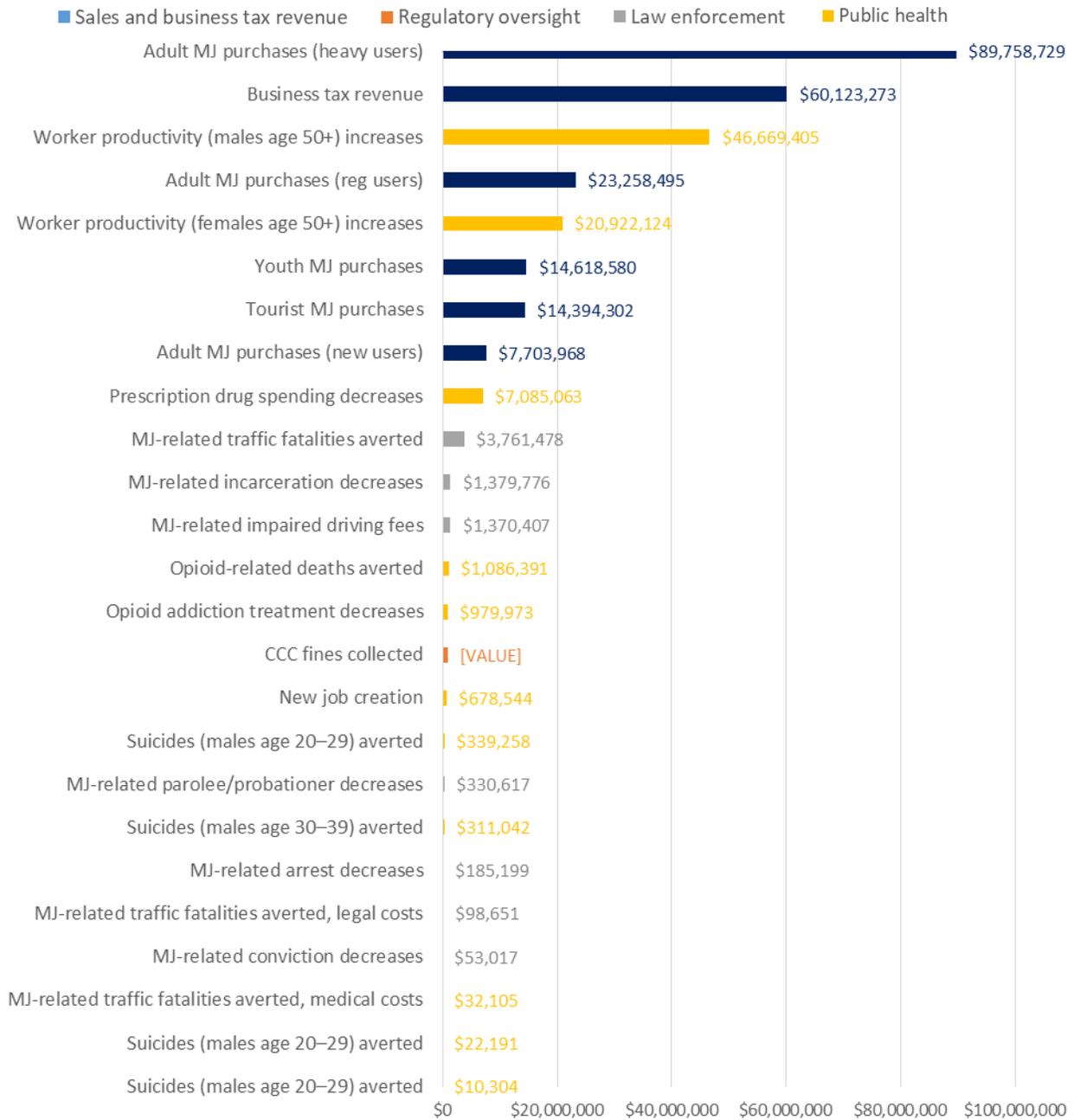
Note: Values in parentheses reflect negative values.

^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

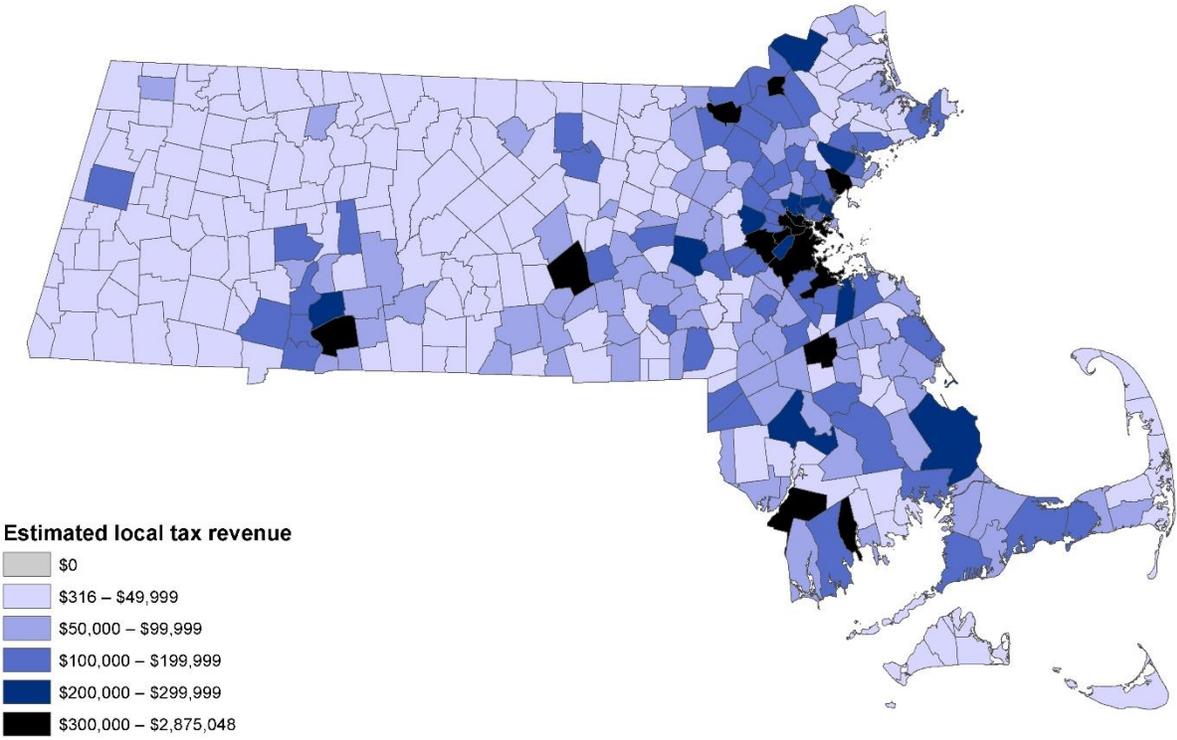


Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

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

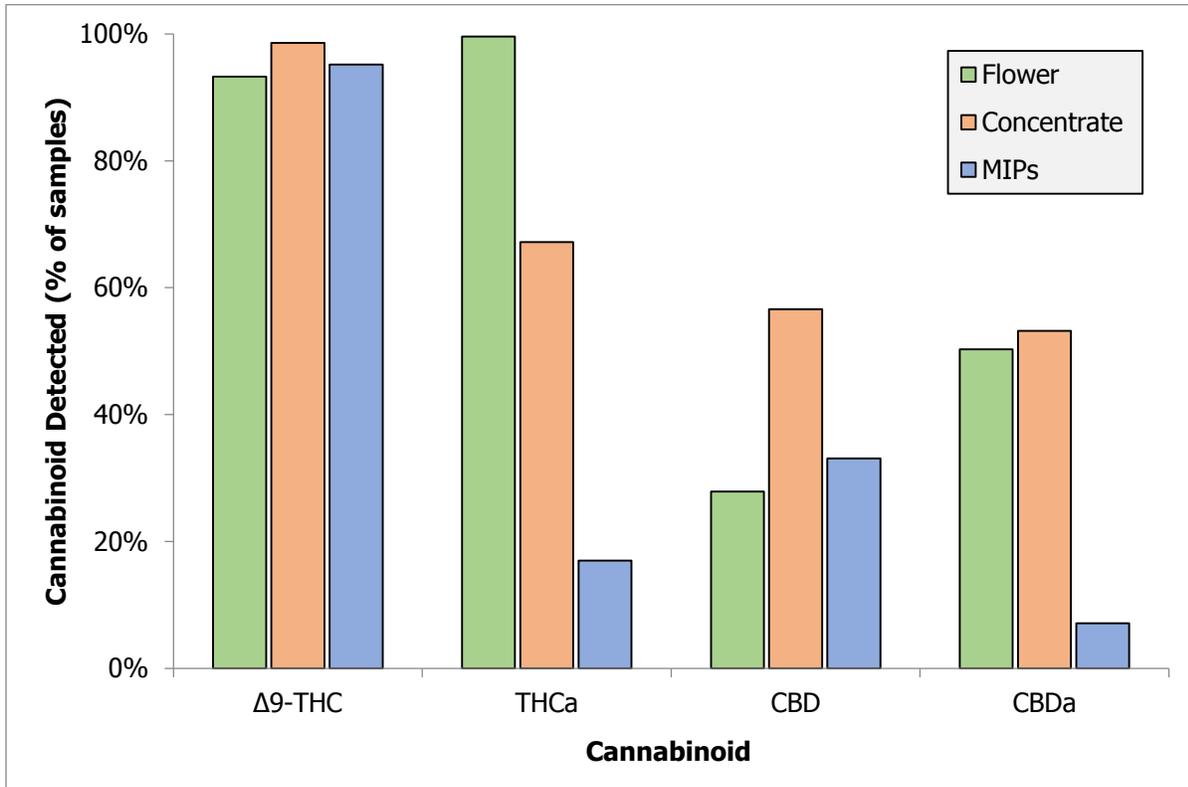


Figure 2: RMD Retail Price Survey*

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 $\geq 30\%$ 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	76.1 (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 $\geq 30\%$ 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	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 ≥ 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	77.5 (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			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 $\geq 30\%$

BENEFITS REPORTED ON THE PATIENT SELF-EVALUATION: PATIENTS WITH FIRST
ENROLLMENT JULY 2015-JUNE 2016

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 $\geq 30\%$ 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	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 ≥ 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	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 $\geq 30\%$ 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	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.

SB174

Measure Title: RELATING TO MEDICAL MARIJUANA.

Report Title: Medical Marijuana; Debilitating Medical Condition

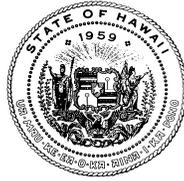
Description: Amends the definition of debilitating medical condition to include lupus, epilepsy, multiple sclerosis, arthritis, autism, anxiety, depression, insomnia, and stress as conditions that qualify for the legal use of medical marijuana.

Companion:

Package: None

Current Referral: CPH, JDL

Introducer(s): ESPERO, ENGLISH, RUDERMAN, S. Chang, Dela Cruz, Gabbard, Galuteria, Kidani



STATE OF HAWAII
DEPARTMENT OF HEALTH
P. O. Box 3378
Honolulu, HI 96801-3378
doh.testimony@doh.hawaii.gov

**Testimony in OPPOSITION to SB174
RELATING TO MEDICAL MARIJUANA**

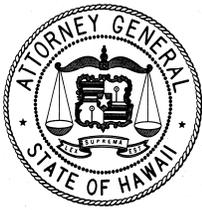
SENATOR ROSALYN H. BAKER, CHAIR
SENATE COMMITTEE ON COMMERCE, CONSUMER PROTECTION, AND HEALTH

Hearing Date: February 8, 2017

Room Number: 229

1 **Fiscal Implications:** None

2 **Department Testimony:** The purpose of this bill is to amend the list of debilitating conditions
3 for the medical use of marijuana by adding a number of new conditions. The Department
4 opposes the passage of new laws related to marijuana until the medical marijuana dispensaries
5 open and we can gauge the impact upon the State. The Department through its Hawaii
6 Administrative Rules §11-160-7 has already laid out a comprehensive annual process to consider
7 addition or deletion of qualifying conditions for the medical use of marijuana. Physicians or
8 potential medical marijuana patients may petition the Department for new conditions. This
9 process will focus on all available medical evidence and research on efficacy and safety for
10 patients. It will include a public hearing where testimony from the public can be provided. The
11 Department has already queried registering physicians and several plan to petition for a variety
12 of conditions. The first annual petition process will be implemented this year. Decisions will be
13 grounded in science that shows that medical marijuana helps treat or relieve any proposed
14 additional conditions.
15 Thank you for the opportunity to testify.



**TESTIMONY OF
THE DEPARTMENT OF THE ATTORNEY GENERAL
TWENTY-NINTH LEGISLATURE, 2017**

ON THE FOLLOWING MEASURE:

S.B. NO. 174, RELATING TO MEDICAL MARIJUANA.

BEFORE THE:

SENATE COMMITTEE ON COMMERCE, CONSUMER PROTECTION, AND HEALTH

DATE: Wednesday, February 8, 2017 **TIME:** 9:00 a.m.

LOCATION: State Capitol, Room 229

TESTIFIER(S): Douglas S. Chin, Attorney General, or
Jill T. Nagamine, Deputy Attorney General

Chair Baker and Members of the Committee:

The Department of the Attorney General opposes this bill. We generally oppose the passage of new laws related to marijuana until the medical marijuana dispensaries open and we get the chance to gauge the impact on the State.

This bill would expand the list of medical conditions for which a patient can be certified for the medical use of marijuana. It would add lupus, epilepsy, multiple sclerosis, arthritis, autism, anxiety, depression, insomnia, and stress to the list of debilitating medical conditions already approved in section 329-121, Hawaii Revised Statutes.

The Attorney General's specific concern about this bill is that, without a scientific or other basis to indicate that the use of marijuana helps treat or provide relief for the additional proposed conditions, the proposed expansion may appear to move the State closer to deregulation of marijuana, a schedule I controlled substance under federal law. Adding so many new conditions, some of which are common and have multiple traditional treatments, could be viewed by the federal government as contrary to the goal of having a robust regulatory scheme for the medical use of marijuana in Hawaii.

We respectfully ask this Committee to hold this bill.



Dedicated to safe, responsible, humane and effective drug policies since 1993

TO: Senate Committee on Commerce, Consumer Protection and Health
FROM: Carl Bergquist, Executive Director
HEARING DATE: 9 February 2017, 9AM
RE: SB174, Relating to Medical Marijuana, **SUPPORT**

Dear Chair Baker, Vice Chair Nishihara, Committee Members:

The Drug Policy Forum of Hawai'i (DPFHI) supports this measure to add various new medical conditions as qualifying for the legal use of medical cannabis in Hawai'i. Several of these conditions are specifically listed by various other states (lupus, autism, multiple sclerosis, arthritis and epilepsy) while the others (anxiety, depression, insomnia or stress) are broad conditions with symptoms that are arguably better relieved with medical cannabis than with various prescription pharmaceutical products.

While we support the Department of Health's ongoing process to set up a petition process to add further conditions – indeed we are planning to help petition for “opiate use disorder” – we see it as a complement to expeditiously adding specific conditions by statute. Accordingly, we respectfully request your support for this bill that can help relieve the suffering of many patients who otherwise may find no relief or risk becoming addicted to more powerful narcotics.

Mahalo for the opportunity to testify.

From: mailinglist@capitol.hawaii.gov
Sent: Monday, February 6, 2017 6:53 PM
To: CPH Testimony
Cc: intrepid.goddess@gmail.com
Subject: Submitted testimony for SB174 on Feb 8, 2017 09:00AM

SB174

Submitted on: 2/6/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Michelle Tippens	Hawaii Veteran's Cannabis Alliance	Support	Yes

Comments: Aloha members of the Senate Committee on Commerce, Consumer Protection, and Health. My name is Michelle Tippens, I am the founder and Executive Director of the Hawaii Veteran's Cannabis Alliance and Legislative Liaison for the Libertarian Party of Hawaii. These comments are regarding measure SB174, heard February 8, 2017 at 9am. As an expert in the field of Criminal Justice (I hold both a BA and MS in the field), specializing in vice and drug crimes, I have a well-documented academic background and demonstrated aptitude in all aspects of the Crime and Justice field, including an extensive knowledge regarding the development of American drug law. Along with this, I am a veteran of the US Army, single mother of 4 and medical marijuana patient. Although I look "healthy" to most people, I not only suffer from PTSD, I also have fibromyalgia, prosthetic neck implants, 5 fractured thoracic vertebrae and several other injuries. I am able to manage all of these conditions with cannabis therapy and was able to discontinue use of a pulmonary walker in 2012, less than two years after beginning cannabis therapy. When examining SB174 it is easy to see this piece of legislation is a positive step toward ensuring patients with severe, debilitating diseases have a full complement of treatment options available to them. Both the HVCA and I feel this legislation reflects the desire of the Hawaiian people to see the medical use of marijuana program expanded to cover more conditions. I personally support this legislation and the HVCA is in support of this legislation, particularly considering many of the conditions mentioned are commonly diagnosed in our veterans.

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

HAWAII EDUCATIONAL ASSOCIATION FOR LICENSED THERAPEUTIC HEALTHCARE

To: Senator Rosalyn Baker, Chair Consumer Protection and Health
Senator Clarence Nishihara, Vice-Chair Consumer Protection and
Health
Members of the Senate Consumer Protection and Health Committee

Fr: Blake Oshiro, Esq. on behalf of the HEALTH Assn.

Re: Testimony in **Support of Senate Bill (SB) 174**

RELATING TO MEDICAL MARIJUANA.

Amends the definition of debilitating medical condition to include lupus, epilepsy, multiple sclerosis, arthritis, autism, anxiety, depression, insomnia, and stress as conditions that qualify for the legal use of medical marijuana.

Dear Chair Baker, Vice-Chair Nishihara, and Members of the Committee:

HEALTH is a recently formed trade association made up of the eight (8) licensed medical marijuana dispensaries under Haw. Rev. Stat. (HRS) Chapter 329D. HEALTH's members are all committed to ensuring the goals of patient safety, product safety and public safety.

We **strongly support** SB174 which adds additional conditions to qualify for the legal use of medical marijuana. Attached, is a list of the state's that allow medical marijuana and the qualifying conditions. See <https://www.leafly.com/news/health/qualifying-conditions-for-medical-marijuana-by-state>

While we note that the range of conditions vary state to state with some more restrictive, some broader, than Hawaii, we think it is important to note that Hawaii was one of the first states to authorize the use of medical marijuana program in 2000. Yet, since that time, the list of conditions remained the same until 2015's Act 241 added "post-traumatic stress disorder."

However, we believe that there is an abundance of evidence to demonstrate and substantiate the medicinal benefits of medical marijuana for certain conditions, including those in this bill.

As with any other medication, a patient has the opportunity to try the product and see if it produces positive results, and weigh that against any negative side-effects. In close collaboration with their physician who provided the certification,

they can then make their own decision whether to continue or discontinue the use of medical marijuana.

Therefore, we support this bill. Thank you for your consideration.

Alaska

Qualifying conditions to become a medical marijuana patient in Alaska include:

- Cancer
- Glaucoma
- HIV/AIDS
- Cachexia (wasting syndrome)
- Pain
- Nausea
- Seizures
- Muscle spasms
- Multiple sclerosis

For a complete list of qualifying conditions and guidelines, please refer to Alaska's application for medical marijuana registry, or catch up on the latest Alaska cannabis news.

Arizona

Qualifying conditions to become a medical marijuana patient in Arizona include:

- Cancer
- Glaucoma
- HIV/AIDS
- Cachexia (wasting syndrome)
- Pain
- Nausea
- Seizures
- Muscle spasms
- Multiple sclerosis
- PTSD

For a complete list of qualifying conditions and guidelines, please refer to the Arizona state legislature concerning medical marijuana, or catch up on the latest Arizona cannabis news.

Arkansas

Qualifying conditions for the Arkansas Medical Marijuana Amendment include:

- Cancer
- Glaucoma
- HIV/AIDS
- Hepatitis C
- ALS or Lou Gehrig's Disease
- Tourette's Syndrome
- Crohn's disease
- PTSD
- Severe arthritis
- Fibromyalgia
- Alzheimer's disease
- A chronic or debilitating disease that produces:
 - Cachexia or wasting syndrome
 - Peripheral neuropathy
 - Intractable pain
 - Severe nausea
 - Seizures

- Severe or persistent muscle spasms

Arkansas' medical marijuana qualifying conditions are currently effective, but licenses for dispensaries will not be accepted until June 1, 2017.

California

Qualifying conditions to become a medical marijuana patient in California include:

- Cancer
- Anorexia
- AIDS
- Chronic pain
- Cachexia
- Persistent muscle spasms, including those associated with multiple sclerosis
- Seizures, including, but not limited to, those associated with epilepsy
- Severe nausea
- Glaucoma
- Arthritis
- Migraines
- Any other chronic or persistent medical symptom that substantially limits the ability of the person to conduct one or more major life activities (as defined by the Americans with Disabilities Act of 1990) or, if not alleviated, may cause serious harm to the patient's safety or physical or mental health

For a complete list of qualifying conditions and guidelines, please refer to [California Proposition 215](#), with revised [Senate Bill 420](#), or catch up on the latest [California cannabis news](#).

Colorado

Although Colorado has implemented a legal recreational cannabis market, it still operates medical marijuana dispensaries for valid patients. Colorado medical marijuana patients still pay standard sales tax on cannabis but are exempt from the high excise taxes and additional state taxes collected from recreational cannabis sales.

Qualifying conditions to become a medical marijuana patient in Colorado include:

- Cancer
- Glaucoma
- HIV/AIDS
- Cachexia (wasting syndrome)
- Persistent muscle spasms
- Seizures
- Severe nausea
- Severe pain

For a complete list of qualifying conditions and guidelines, please refer to [Colorado's Debilitating Conditions for Medical Marijuana Use](#), or catch up on the latest [Colorado cannabis news](#).

Connecticut

Qualifying conditions to become a medical marijuana patient in Connecticut include:

- Cancer
- Glaucoma
- HIV/AIDS
- Parkinson's disease
- Multiple sclerosis

- Damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity
- Epilepsy
- Cachexia (wasting syndrome)
- Wasting syndrome
- Crohn's disease
- Post-traumatic stress disorder (PTSD)

For a complete list of qualifying conditions and guidelines, please refer to [Connecticut's medical marijuana qualification requirements](#), or catch up on the latest [Connecticut cannabis news](#).

Delaware

Qualifying conditions to become a medical marijuana patient in Delaware include:

- Cancer
- HIV/AIDS
- Hepatitis C
- Lou Gehrig's disease (amyotrophic lateral sclerosis, or ALS)
- Alzheimer's
- Post-traumatic stress disorder (PTSD)
- Cachexia (wasting syndrome)
- Intractable nausea
- Seizures
- Muscle spasms
- Multiple sclerosis

For a complete list of qualifying conditions and guidelines, please refer to [Delaware's medical marijuana program guidelines](#), or catch up on the latest [Delaware cannabis news](#).

District of Columbia (Washington, D.C.)

Qualifying conditions to become a medical marijuana patient in Washington, D.C. include:

- HIV/AIDS
- Cancer
- Glaucoma
- Muscle spasms
- Multiple sclerosis
- Lou Gehrig's disease (ALS)
- Cachexia (wasting syndrome)
- Decompensated cirrhosis
- Alzheimer's
- Seizure disorders
- Any condition diagnosed as "debilitating" by a licensed physician

For a complete list of qualifying conditions and guidelines, please refer to the [District of Columbia's Medical Marijuana Program Patient FAQ](#), or catch up on the latest [Washington, D.C. cannabis news](#).

Florida

Qualifying conditions to become a medical marijuana patient in Florida include:

- Cancer
- Epilepsy
- Glaucoma
- HIV/AIDS

- PTSD
- ALS or Lou Gehrig's disease
- Crohn's disease
- Parkinson's disease
- Multiple sclerosis

For more information on the Florida Medical Marijuana Legalization, please refer to Amendment 2.

Georgia

Georgia only allows for the use of low THC oil (less than 5% THC by weight).

Qualifying conditions to become a medical marijuana patient in Georgia include:

- Cancer
- Lou Gehrig's disease (ALS)
- Seizure disorders related to diagnosis of epilepsy or trauma-related head injuries
- Multiple sclerosis
- Crohn's disease
- Mitochondrial disease
- Parkinson's disease
- Sickle cell disease

For a complete list of qualifying conditions and guidelines, please refer to House Bill 1 (Haleigh's Hope Act), or catch up on the latest [Georgia cannabis news](#).

Hawaii

Qualifying conditions to become a medical marijuana patient in Hawaii include:

- Cancer
- Glaucoma
- HIV/AIDS
- Cachexia (wasting syndrome)
- Pain
- Nausea
- Seizures
- Muscle spasms
- Multiple sclerosis

For a complete list of qualifying conditions and guidelines, please refer to Hawaii Senate Bill 862, or catch up on the latest [Hawaii cannabis news](#).

Illinois

Qualifying conditions to become a medical marijuana patient in Illinois include:

- Acquired Immunodeficiency Syndrome (AIDS)
- Alzheimer's disease
- Lou Gehrig's disease (ALS)
- Arnold-Chiari malformation and syringomyelia
- Cachexia/wasting syndrome
- Cancer
- Causalgia
- Chronic inflammatory demyelinating polyneuropathy
- Crohn's disease
- CRPS (Complex Regional Pain Syndrome Type I)
- CRPS (Complex Regional Pain Syndrome Type II)

- Dystonia
- Fibromyalgia (severe)
- Fibrous dysplasia
- Glaucoma
- Hepatitis C
- Human Immunodeficiency Virus (HIV)
- Hydrocephalus
- Hydromyelia
- Interstitial cystitis
- Lupus
- Multiple sclerosis
- Muscular dystrophy
- Myasthenia gravis
- Myoclonus
- Nail-patella syndrome
- Neurofibromatosis
- Parkinson's disease
- Post-concussion syndrome
- Post-Traumatic Stress Disorder (PTSD)
- Reflex sympathetic dystrophy
- Residual limb pain
- Rheumatoid arthritis (RA)
- Seizures
- Sjogren's syndrome
- Spinal cord disease (including but not limited to arachnoiditis, Tarlov cysts, hydromyelia & syringomyelia)
- Spinal cord injury
- Spinocerebellar ataxia (SCA)
- Syringomyelia
- Tarlov cysts
- Tourette syndrome
- Traumatic brain injury (TBI)

For a complete list of qualifying conditions and guidelines, please refer to the [Illinois Medical Cannabis Pilot Program's FAQ](#), or catch up on the [latest Illinois cannabis news](#).

Iowa

Iowa allows for the use of high-CBD cannabis extracts with less than .3% THC.

Qualifying conditions to become a medical marijuana patient in Iowa include:

- Intractable epilepsy

For a complete list of guidelines, please refer to [Iowa Medical Cannabidiol Act Quick Facts](#), or catch up on the [latest Iowa cannabis news](#).

Kentucky

Kentucky allows for the use of low-THC cannabis or industrial hemp-derived CBD oil. Only those who are participating in a clinical trial or expanded access program are legally allowed to possess CBD oil.

For more information on accessing CBD in Kentucky, please refer to [Senate Bill 124](#), or catch up on the [latest Kentucky cannabis news](#).

Louisiana

Qualifying conditions to become a medical marijuana patient in Louisiana include:

- Symptoms related to cancer
- Glaucoma
- Spastic quadriplegia

For more information on Louisiana's medical marijuana law, please refer to [Senate Bill 143](#), or catch up on the latest [Louisiana cannabis news](#).

Maine

Qualifying conditions to become a medical marijuana patient in Maine include:

- Chronic pain that has not responded to conventional therapy for more than six months
- Post-traumatic stress disorder (PTSD)
- Lou Gehrig's disease (ALS)
- Alzheimer's
- Cachexia (wasting syndrome)
- Cancer
- Crohn's disease
- Glaucoma
- Hepatitis C (active form)
- HIV
- Inflammatory bowel disease (IBS)
- Seizure disorders
- Severe muscle spasms (including multiple sclerosis and other diseases causing severe and persistent muscle spasms)
- Severe nausea

For a complete list of qualifying conditions and guidelines, please refer to [Maine's medical use of marijuana guidelines](#), or catch up on the latest [Maine cannabis news](#).

Maryland

Qualifying conditions to become a medical marijuana patient in Maryland include:

- Cachexia (wasting syndrome)
- Severe, debilitating, or chronic pain
- Severe nausea
- Seizures, including those characteristic of epilepsy
- Severe and persistent muscle spasms
- Multiple sclerosis
- Crohn's disease
- Alzheimer's
- Cancer
- Glaucoma
- HIV/AIDS
- Hepatitis C

For a complete list of qualifying conditions and guidelines, please refer to [Maryland Senate Bill 757](#), or catch up on the latest [Maryland cannabis news](#).

Massachusetts

Qualifying conditions to become a medical marijuana patient in Massachusetts include:

- Cancer

- Glaucoma
 - AIDS
 - Hepatitis C
 - Lou Gehrig's disease (ALS)
 - Crohn's disease
 - Parkinson's disease
 - Multiple sclerosis
 - Other debilitating conditions as determined in writing by a qualifying patient's certifying physician.
- For a complete list of qualifying conditions and guidelines, please refer to the [Massachusetts medical use of marijuana overview](#), or catch up on the latest [Massachusetts cannabis news](#).

Michigan

Qualifying conditions to become a medical marijuana patient in Michigan include:

- Cancer
- Glaucoma
- HIV/AIDS
- Hepatitis C
- Lou Gehrig's disease (Amyotrophic lateral sclerosis, or ALS)
- Alzheimer's
- Nail-patella syndrome
- Cachexia (wasting disease)
- Severe and chronic pain
- Severe nausea
- Seizures
- Epilepsy
- Muscle spasms
- Multiple sclerosis

For a complete list of qualifying conditions and guidelines, please refer to the [Michigan Medical Marihuana Registry Program FAQ](#), or catch up on the latest [Michigan cannabis news](#).

Minnesota

Minnesota does not allow for smokeable cannabis, only a 30-day supply of oils, edibles, and concentrates. Qualifying conditions to become a medical marijuana patient in Minnesota include:

- Lou Gehrig's disease (Amyotrophic lateral sclerosis, or ALS)
- Cancer
- Cachexia
- Crohn's disease
- Glaucoma
- HIV/AIDS
- Seizures
- Severe and persistent muscle spasms
- Terminal illness
- Tourette syndrome
- Intractable pain*

*Recently recommended qualifying condition soon to be available for Minnesota patients.

For more information, please visit the [Minnesota Department of Health – Medical Cannabis](#), or catch up on the latest [Minnesota cannabis news](#).

Mississippi

Mississippi allows access to CBD oil only. Qualifying conditions to become a medical marijuana patient in Mississippi include:

- Debilitating epileptic seizure disorders

Patients must receive medical recommendations by a physician from the University of Mississippi Medical Center to participate in the clinical trial. For more information, please refer to [House Bill 1231](#) or [Harper Grace's Law](#), or catch up on the latest [Mississippi cannabis news](#).

Missouri

Missouri allows access to CBD oil only. Qualifying conditions to become a medical marijuana patient in Missouri include:

- Intractable epilepsy

For more information, please refer to [House Bill 2238](#), or catch up on the latest [Missouri cannabis news](#).

Montana

Qualifying conditions to become a medical marijuana patient in Montana include:

- Cancer
- Glaucoma
- HIV/AIDS
- Cachexia (wasting syndrome)
- Chronic pain
- Intractable nausea or vomiting
- Epilepsy or an intractable seizure disorder
- Multiple sclerosis
- Crohn's disease
- Painful peripheral neuropathy
- A central nervous system disorder resulting in chronic, painful spasticity or muscle spasms

For a complete list of qualifying conditions and guidelines, please refer to [Montana Code Annotated 2013](#), or catch up on the latest [Montana cannabis news](#).

Nevada

Qualifying conditions to become a medical marijuana patient in Nevada include:

- AIDS
- Cancer
- Glaucoma
- Condition or treatment for a medical condition that produces cachexia (general physical wasting and malnutrition)
- Persistent muscle spasms (including multiple sclerosis)
- Seizures (including epilepsy)
- Severe nausea
- Severe pain

For a complete list of qualifying conditions and guidelines, please refer to the [Nevada Medical Marijuana Program](#), or catch up on the latest [Nevada cannabis news](#).

New Hampshire

Qualifying conditions to become a medical marijuana patient in New Hampshire include:

- A chronic or terminal disease
- Cachexia (wasting syndrome)

- Severe pain
- Severe nausea/vomiting
- Seizures
- Severe, persistent muscle spasms

For a complete list of qualifying conditions and guidelines, please refer to [New Hampshire House Bill 573](#), or catch up on the latest [New Hampshire cannabis news](#).

New Jersey

Qualifying conditions to become a medical marijuana patient in New Jersey include:

- Lou Gehrig's disease (amyotrophic lateral sclerosis, or ALS)
- Multiple sclerosis
- Terminal cancer
- Muscular dystrophy
- Inflammatory bowel disease (IBS)
- Crohn's disease
- Terminal illness if the physician has determined a prognosis of less than 12 months of life
- Seizure disorder, including epilepsy
- Intractable skeletal muscular spasticity
- Glaucoma
- HIV/AIDS
- Cancer

For a complete list of qualifying conditions and guidelines, please refer to the [New Jersey Medicinal Marijuana Program](#), or catch up on the latest [New Jersey cannabis news](#).

New Mexico

Qualifying conditions to become a medical marijuana patient in New Mexico include:

- Severe chronic pain
- Painful peripheral neuropathy
- Intractable nausea/vomiting
- Severe anorexia
- Cachexia (wasting syndrome)
- Hepatitis C infection currently receiving antiviral treatment
- Crohn's disease
- Post-traumatic stress disorder (PTSD)
- Lou Gehrig's disease (amyotrophic lateral sclerosis, or ALS)
- Cancer
- Glaucoma
- Multiple sclerosis
- Damage to the nervous tissue of the spinal cord with intractable spasticity
- Epilepsy
- HIV/AIDS
- Inflammatory autoimmune-mediated arthritis
- Hospice patients

For a complete list of qualifying conditions and guidelines, please refer to the [New Mexico Medical Cannabis Program FAQ](#), or catch up on the latest [New Mexico cannabis news](#).

New York

Qualifying conditions to become a medical marijuana patient in New York include:

- Cancer
- Epilepsy
- HIV/AIDS
- Huntington's disease
- Inflammatory Bowel Disease (IBS)
- Lou Gehrig's disease (ALS)
- Parkinson's disease
- Multiple sclerosis (MS)
- Neuropathies
- Spinal cord damage

For a complete list of qualifying conditions and guidelines, please refer to the [New York State Medical Marijuana Program FAQ](#), or catch up on the [latest New York cannabis news](#).

North Carolina

North Carolina allows for the use of CBD oil only. Qualifying conditions to become a medical marijuana patient in North Carolina include:

- Intractable epilepsy

For more information, please refer to [House Bill 1220](#), or catch up on the [latest North Carolina cannabis news](#).

North Dakota

North Dakota's qualifying conditions for the North Dakota Compassionate Care Act include:

- Cancer and its treatments
- HIV/AIDS
- Hepatitis C
- ALS or Lou Gehrig's disease
- PTSD
- Alzheimer's disease, dementia, or treatment of these conditions
- Crohn's disease
- Fibromyalgia
- Spinal stenosis
- Chronic back pain, including:
 - Neuropathy or damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity
- Glaucoma
- Epilepsy
- A chronic or debilitating disease, medical condition, or its treatment that produces one or more of the following:
 - Cachexia or wasting syndrome
 - Severe, debilitating pain that has not responded to previously prescribed medication or surgical measures for more than three months or for which other treatment options produced serious side effects
 - Intractable nausea
 - Seizures
 - Severe or persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis.

For more information, please refer to the [North Dakota Compassionate Care Act](#).

Oklahoma

Oklahoma allows for the use of CBD oil only. Qualifying conditions to become a medical marijuana patient in Oklahoma include:

- Must be under the age of 18 suffering from:
 - Lennox-Gastaut syndrome
 - Dravet syndrome
 - Severe myoclonic epilepsy of infancy
 - Any form of refractory epilepsy not treatable by traditional medical therapies

For more information, please refer to [Katie and Cayman's Law \(House Bill 2154\)](#), or catch up on the latest [Oklahoma cannabis news](#).

Oregon

Qualifying conditions to become a medical marijuana patient in Oregon include:

- Cancer
- Glaucoma
- Alzheimer's
- HIV/AIDS
- Cachexia (wasting syndrome)
- Severe pain
- Severe nausea
- Seizures, including but not limited to seizures caused by epilepsy
- Persistent muscle spasms
- Multiple sclerosis

For a complete list of qualifying conditions and guidelines, please refer to the [Oregon Medical Marijuana Act](#), or catch up on the latest [Oregon cannabis news](#).

Pennsylvania

Qualifying conditions to become a medical marijuana patient in Pennsylvania include:

- Cancer
- HIV/AIDS
- Amyotrophic Lateral Sclerosis (ALS)
- Parkinson's Disease
- Multiple sclerosis
- Damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity
- Epilepsy
- Inflammatory bowel disease (IBS)
- Neuropathies
- Huntington's disease
- Post-traumatic stress disorder (PTSD)
- Intractable seizures
- Glaucoma
- Sickle cell anemia
- Severe, chronic or intractable pain of neuropathic origin or severe chronic or intractable pain in which conventional therapeutic intervention and opiate therapy is contraindicated or ineffective
- Autism
- "Terminally ill" – a medical prognosis or life expectancy of approximately one year or less if the illness runs its normal course.

For more information, please refer to [Senate Bill 3](#).

Rhode Island

Qualifying conditions to become a medical marijuana patient in Rhode Island include:

- Cancer
- Glaucoma
- HIV/AIDS
- Hepatitis C
- Cachexia (wasting syndrome)
- Chronic pain
- Severe nausea
- Seizures, including but not limited to those characteristic of epilepsy
- Severe and persistent muscle spasms
- Multiple sclerosis
- Crohn's disease
- Alzheimer's

For a complete list of qualifying conditions and guidelines, please refer to Rhode Island's medical marijuana approved qualifying debilitating medical conditions, or catch up on the latest Rhode Island cannabis news.

South Carolina

South Carolina allows for the use of CBD oil only. Qualifying conditions to become a medical marijuana patient in South Carolina include:

- Certain forms of epilepsy as part of a state-run clinical trial

For more information, please refer to the Medical Cannabis Therapeutic Treatment Research Act, or catch up on the latest South Carolina cannabis news.

Tennessee

Tennessee allows for the use of CBD oil only. Qualifying conditions to become a medical marijuana patient in Tennessee include:

- Intractable seizures (as part of a clinical research study)

For more information, please refer to Senate Bill 280, or catch up on the latest Tennessee cannabis news.

Texas

Texas allows for the use of CBD oil only. Qualifying conditions to become a medical marijuana patient in Texas include:

- Intractable epilepsy

For more information, please refer to Senate Bill 339, or catch up on the latest Texas cannabis news.

Utah

Utah allows for the use of CBD oil only. Qualifying conditions to become a medical marijuana patient in Utah include:

- Intractable epilepsy

For more information, please refer to House Bill 105, or catch up on the latest Utah cannabis news.

Vermont

Qualifying conditions to become a medical marijuana patient in Vermont include:

- Cancer
- AIDS/HIV
- Multiple sclerosis

- Cachexia (wasting syndrome)
- Severe pain
- Nausea
- Seizures

For a complete list of qualifying conditions and guidelines, please refer to the [Vermont patient marijuana registry FAQ](#), or catch up on the latest [Vermont cannabis news](#).

Washington

Changes to Washington state's marijuana laws via Senate Bill 5052 will result in the state's medical marijuana industry being absorbed by its recreational cannabis market. These changes will go into full effect July 1, 2016. Until then, medical marijuana dispensaries will still be operational but are ultimately expected to close or incorporate themselves into an existing licensed retail cannabis shop.

Qualifying conditions to become a medical marijuana patient in Washington include:

- Cancer
- HIV/AIDS
- Multiple sclerosis
- Epilepsy or other seizure disorder
- Spasticity disorders
- Intractable pain
- Glaucoma
- Crohn's disease
- Hepatitis C
- Diseases, including anorexia, which result in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity

For a complete list of qualifying conditions and guidelines, please refer to the [Washington state legislature regarding medical cannabis](#), or catch up on the latest [Washington state cannabis news](#).

Wisconsin

Wisconsin allows for the use of non-psychoactive CBD oil only. Qualifying conditions to become a medical marijuana patient in Wisconsin include:

- Seizure disorders

For more information, please refer to [Lydia's Law \(Act 267\)](#), or catch up on the latest [Wisconsin cannabis news](#).

Wyoming

Wyoming allows for the use of CBD oil only. Qualifying conditions include:

- Intractable epilepsy

For more information, please refer to [House Bill 32](#), or catch up on the latest [Wyoming cannabis news](#).



ON THE FOLLOWING MEASURE:

SB174, RELATING TO MEDICAL MARIJUANA

BEFORE THE:

SENATE COMMITTEE ON COMMERCE, CONSUMER PROTECTION,
AND HEALTH

DATE: Wednesday, February 8, 2017

TIME: 9:00 a.m.

LOCATION: State Capitol, Conference Room 229

TESTIFIER: Christopher Garth, Executive Director

Honorable Chair Baker and Members of the Committee:

The Hawai'i Dispensary Alliance submits the following testimony in **SUPPORT of SB174 RELATING TO MEDICAL MARIJUANA**, which amends the definition of debilitating medical condition to include lupus, epilepsy, multiple sclerosis, arthritis, autism, anxiety, depression, insomnia, and stress as conditions that qualify for the legal use of medical marijuana.

The Hawaii Dispensary Alliance is a patient-centric organization that aims to appropriately introduce the legitimate cannabis industry to the state of Hawaii. Our membership is drawn from patients and caregivers, ancillary businesses related to and involved in the physical and intellectual cannabis space, and those who generally support the value of a legal right to cannabis-based medicine. The Alliance has established itself as a consistent voice in the conversation for greater patient access to safe and quality cannabis resources; and it is from this perspective that we support SB174.

Our board and membership find that the language of this measure will provide greater access to less invasive medical solutions, by expanding the applicability of cannabis-based medicine. If passed, this measure will place Hawaii on the list of states as one of the more inclusive state regulated medical cannabis programs in the nation. Including these qualifying conditions on our roster would benefit future medical cannabis studies conducted by the University of Hawaii system as well as those conducted in private by local firms. This is an opportunity to help more patients and to conduct the sound medical research the international medical cannabis industry desperately needs.

For all of the foregoing reasons, the Hawai'i Dispensary Alliance **SUPPORTS** the language of this measure and recommends that **SB174** be moved forward for further discussion.

A 2016 version of a state-by-state list of qualifying conditions has been attached for your review and comparison. This list has been vetted and approved by the State of Hawaii Department of Health.

Thank you very much for the opportunity to provide testimony on this measure.

Qualifying Ailments by State*

	Alaska	Arizona	California	Colorado	Connecticut	Delaware	Hawaii	Illinois	Maine	Maryland	Massachusetts	Michigan	Minnesota	Montana	Nevada	New Hampshire	New Jersey	New Mexico	New York	Oregon	Rhode Island	Vermont	Washington DC	Washington State
ALS	+				+		+	+		+	+	+			+	+	+	+						
Alzheimer's	+				+		+	+		+	+	+			+	+	+	+		+	+			
Anorexia		+							+						+	+								
Arnold Chiari Malformation							+																	
Arthritis		+					+									+								
Brain Injury/Concussion							+								+									+
Cachexia	+	+	+	+	+		+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+
Cancer	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Causalgia							+																	
Cervical Dystonia																+								
Chronic Spasticity												+												
Chronic Pancreatitis															+									
Crohn's	+			+		+	+	+	+	+	+	+	+		+	+	+						+	
CRPS							+																	
Dystonia							+																	
Epilepsy			+		+	+				+		+			+	+	+	+						+
Fibromyalgia							+																	
Fibrous Dysplasia							+																	
Glaucoma	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatitis C		+			+		+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+
HIV/AIDS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hospice Patients								+				+				+								
Huntington's																+	+							
Hydrocephalus							+																	
Hydromyelia							+																	
Inclusion Body Myositis																+								
Inflammatory Bowel																+		+						
Interstitial Cystitis							+																	
Intractable Pain												+				+	+	+						+
Lupus							+								+									
Migraines		+																						
Multiple Sclerosis				+	+	+	+		+			+	+	+	+	+	+	+		+	+	+	+	+
Muscular Dystrophy							+								+									
Myasthenia Gravis							+																	
Myoclonus							+																	
Nail Patella Syndrome							+	+		+														
Neurofibromatosis							+																	
Neuropathy							+					+				+	+							
Palliative Care																								
Parkinson's				+		+	+		+						+	+	+							
PTSD				+	+	+		+	+		+			+		+		+						+
Residual Limb Pain							+																	
RSD							+																	
Sjogren's Syndrome							+																	
Seizures	+	+	+	+		+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Severe Nausea	+	+	+	+		+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Severe Muscle Spasms	+	+	+	+			+	+		+	+	+	+	+	+			+	+	+	+	+	+	+
Severe & Chronic Pain	+	+	+	+		+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Severe Vomiting												+	+		+									+
Spinal Cord Injury				+			+								+		+	+						
Spinocerebellar Ataxia							+																	
Syringomyelia							+																	
Tarlov Cysts							+																	
Terminal Patients											+				+									
Treatments: Chemotherapy, Radiotherapy, Azidothymidine, Protease Inhibitors																							+	
Tourette's Syndrome							+				+													
Ulcerative Colitis																+								
Weakness									+								+							
Wasting Syndrome	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

*Last updated Nov. 2016. Check with your local doctor to see if your medical condition qualifies. In some states, a patient must exhibit more than one of the listed conditions to qualify.

PO Box 893900
Mililani, HI 96789
(808) 397-0241



SB174

RELATING TO MEDICAL MARIJUANA

Senate Committee on Commerce, Consumer Protection, and Health

Wednesday February 8, 2017

9:00 AM

State Capitol, Conference Room 229

Aloha Chair Baker, Vice Chair Nishihara, and Members of the Committee,

Pakalōlō Suite, a Hawai'i based community organization of qualified medical marijuana patients, STRONGLY SUPPORTS SB174. SB174 would amend the definition of “debilitating medical condition” to include lupus, epilepsy, multiple sclerosis, arthritis, autism, anxiety, depression, insomnia, and stress.”

The medical use of marijuana has provided comfort and relief to countless individuals suffering from medical conditions that they would undoubtedly define as “debilitating.” However, state laws have narrowly defined, or left ambiguous, those qualifying medical conditions necessary to become a qualified medical marijuana patient. Cannabidiol, or CBD, a non-psychoactive compound of marijuana (cannabis), has gained momentum in its positive treatment of the debilitating symptoms of neurodevelopmental disorders like autism or neurological disorders like epilepsy – two medical conditions enumerated in SB174’s expanded definition of “debilitating medical condition.”

The state’s progression toward a compassionate approach to the medical use of marijuana has authorized the licensing and establishment of medical marijuana dispensaries. Individuals suffering from debilitating medical conditions now have greater access to proven medical treatment. By expanding the definition of “debilitating medical condition,” the state would provide greater access to medical treatment for a much larger group of people in need.

Mahalo nui loa for this opportunity to share our testimony,

Māhealani Traub
Pakalōlō Suite Prime Advocate

February 6, 2017

Senator Rosalyn H. Baker
Chair, Senate Committee on
Commerce, Consumer Protection,
and Health
Hawaii State Senate
Hawaii State Capitol, Room 230

Senator Clarence K. Nishihara
Vice Chair, Senate Committee on
Commerce, Consumer Protection, and
Health
Hawaii State Senate
Hawaii State Capitol, Room 214

RE: **SB174 – Support**

Senator Baker and Senator Nishihara,

My name is Robert Wiedmeyer, and I have been a resident of Waikoloa, Hawaii for two and a half years. My legislators are Representative Cindy Evans and Senator Lorraine Inouye.

I am writing to express my support for SB174, which amends the definition of debilitating medical conditions to include lupus, epilepsy, multiple sclerosis, arthritis, autism, anxiety, depression, insomnia, and stress as conditions that qualify for the legal use of medical marijuana.

SB174 takes positive steps toward updating Hawaii law to enhance access to a safe, effective medication for a number of serious and sometimes chronic medical conditions. When used under the supervision of a qualified medical professional, cannabis has been shown to help relieve these conditions and potentially allow patients to reduce reliance on opiates and other medicines that have potentially serious, harmful side effects.

With the state's dispensaries set to open in the near future, this is the time to expand legal access to more patients who stand to benefit from cannabis-based medicine.

I appreciate your thoughtful consideration of this legislation.

Sincerely,
Robert Wiedmeyer

PATIENTS WITHOUT TIME

February 7, 2017

TO: HAWAII STATE LEGISLATURE

TESTIMONY

Aloha Legislators,

LEGALIZE MARIJUANA NOW!

SAVE LIVES! 90,000 Americans die from alcohol every year, yet Hawaii celebrates the success of Hawaii's wineries and microbreweries. Tourists are encouraged to visit production centers and tasting rooms. Meanwhile, requiring cannabis production centers to have 24/7 video surveillance, and concealment from the public view. This is unfounded prejudice and paranoia. The CDC states marijuana kills ZERO Americans, so why the prejudice against it?

For 16 years, Hawaii has practiced **SELECTIVE PROSECUTION** against marijuana consumers. Protecting some folks with "329 cards" from prosecution (stating that marijuana is medicine), while sending others to jail for "marijuana crimes," (stating marijuana has no medical value). There exists a clear, facial contradiction between marijuana's classification as a schedule I drug and its allowable use by qualifying patients for medical conditions.

The only just solution is to legalize marijuana. Tax and regulate Hawaii's estimated \$billion-plus dollar-a-year illegal marijuana industry, and raise a \$100-million-plus dollars-a-year in revenue, decrease expenses fighting the failed prohibition, clear court dockets, save families broken by incarceration, and create thousands of new legal jobs and business. WIN- WIN -WIN

Mahalo for your kind consideration,

PATIENTS WITHOUT TIME, Maui, HI, submitted by Brian Murphy, Director

From: mailinglist@capitol.hawaii.gov
Sent: Monday, February 6, 2017 1:08 PM
To: CPH Testimony
Cc: wao-hsl@WeAreOne.cc
Subject: *Submitted testimony for SB174 on Feb 8, 2017 09:00AM*

SB174

Submitted on: 2/6/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Joseph Kohn MD	Individual	Support	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

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From: mailinglist@capitol.hawaii.gov
Sent: Monday, February 6, 2017 6:49 AM
To: CPH Testimony
Cc: mary@mauivortex.com
Subject: Submitted testimony for SB174 on Feb 8, 2017 09:00AM

SB174

Submitted on: 2/6/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Mary Overbay	Individual	Oppose	No

Comments: Aloha Senators, LEGALIZE MARIJUANA NOW! 90,000 Americans die from alcohol every year, yet Hawaii celebrates the success of microbreweries, and allows tourists access to production centers, and tasting rooms! Marijuana consumers demand equal rights! Since Marijuana kills ZERO Americans, why the prejudice against it, in favor of highly addictive and deadly alcohol? LEGALIZE MARIJUANA NOW! For 16 years, Hawaii has practiced SELECTIVE PROSECUTION against marijuana consumers. Protecting some folks from prosecuting, while sending others to jail for "marijuana crimes." LEGALIZE MARIJUANA and SAVE LIVES!

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From: mailinglist@capitol.hawaii.gov
Sent: Thursday, February 2, 2017 8:20 PM
To: CPH Testimony
Cc: ncsugano@gmail.com
Subject: *Submitted testimony for SB174 on Feb 8, 2017 09:00AM*

SB174

Submitted on: 2/2/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Jari S.K. Sugano	Individual	Support	No

Comments:

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From: mailinglist@capitol.hawaii.gov
Sent: Thursday, February 2, 2017 5:18 PM
To: CPH Testimony
Cc: mendezj@hawaii.edu
Subject: *Submitted testimony for SB174 on Feb 8, 2017 09:00AM*

SB174

Submitted on: 2/2/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Javier Mendez-Alvarez	Individual	Support	No

Comments:

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From: mailinglist@capitol.hawaii.gov
Sent: Tuesday, February 7, 2017 3:24 AM
To: CPH Testimony
Cc: dsusott@gmail.com
Subject: Submitted testimony for SB174 on Feb 8, 2017 09:00AM

SB174

Submitted on: 2/7/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
daniel susott, md, mph	Individual	Support	Yes

Comments: Mahalo for doing the right thing here. If that is still unclear to you, please get informed. It's time, it's important, and it's your job. Aloha and blessings

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From: mailinglist@capitol.hawaii.gov
Sent: Tuesday, February 7, 2017 1:17 AM
To: CPH Testimony
Cc: joe.kelsoe@gmail.com
Subject: Submitted testimony for SB174 on Feb 8, 2017 09:00AM

SB174

Submitted on: 2/7/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Joe Bradley Kelsoe II	Individual	Support	Yes

Comments: I will be showing support for this bill, and encourage the session to progress on and forward as we press into the future of Medical Marijuana in Hawaii.

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

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From: mailinglist@capitol.hawaii.gov
Sent: Tuesday, February 7, 2017 12:05 AM
To: CPH Testimony
Cc: fehren.jones@gmail.com
Subject: Submitted testimony for SB174 on Feb 8, 2017 09:00AM

SB174

Submitted on: 2/7/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
fehren	Individual	Support	No

Comments: Aloha. My name is Fehren Jones, I reside in the Honolulu area. I am in full support of SB174 which states that "Amends the definition of debilitating medical condition to include lupus, epilepsy, multiple sclerosis, arthritis, autism, anxiety, depression, insomnia, and stress as conditions that qualify for the legal use of medical marijuana." At the moment, no, I do not have any of these serious health conditions, but, I am starting to feel the arthritis, it comes with age. I do come across anxiety from time to time and the daily stress, but who doesn't come across stress and anxiety from time to time? I am a medical marijuana card holder and, yes, I do use my medical marijuana medicine when these symptoms arrive and IT DOES HELP. As for the lupus, epilepsy, and multiple sclerosis I do not know what it feels like to go through those uncomfortable diseases/sickness but I have read numerous of articles and I have watched many shows on how medical marijuana have helped countless of individuals get through the day, and to just getting through the day is a milestone for many of these ones. Mahalo for your time and patients. I'm sure its not easy to read every single testimony that's submitted. I appreciate the time that you spend on going through it all.

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

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D. DOUGLAS SMITH, M.D.
229 Aiokoa Street
KAILUA, HAWAII 96734

February 7, 2016 at 9:00 AM

Room 229

To: COMMITTEE ON COMMERCE, CONSUMER PROTECTION & HEALTH
Senator Rosalyn H. Baker, Chair
Senator Clarence K. Nishihara, Vice Chair

From: D. Douglas Smith, M.D.

Re: SB 174, Relating to Medical Marijuana

IN OPPOSE

I would like to thank Chair Baker, Vice Chair Nishihara, and members of the Senate Committee on Commerce, Consumer Protection and Health for the opportunity to submit comments on SB174.

I am a physician who specializes in psychiatry and have spent my career practicing in Hawaii. For 11 years I was on the faculty of the JABSOM department of psychiatry and I treated patients and supervised residents at the Hawaii State Hospital and Queens Medical Center. I have also worked in private practice and with the Adult Mental Health Division's Assertive Community Treatment Program.

I oppose this bill, and urge you to reconsider some of its important health implications for access to mental health care in Hawaii.

SB174 would expand the definition of "debilitating medical conditions" that qualify for the legal use of medical marijuana to include "autism, anxiety, depression, insomnia, and stress as conditions." This is reckless expansion of qualifying diagnoses flies in the face of clinical experience and available medical literature. It would be a regrettable health policy that promises to add to the burdens on our strained mental health system.

The 2013 position statement of the American Psychiatric Association (APA) is clear in this regard. It states, "There is no current scientific evidence that marijuana is in any way

beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development.” (see attachment)

Before authorizing this legislation, committee members should consider the evidence of limited benefit and serious mental health risks posed by high-potency medical cannabis, including its association with an increased incidence and worse outcomes for Depression, Bipolar disorder, Schizophrenia and other psychotic conditions. As the referenced APA resource document concludes:

There is currently no scientific evidence to support the use of marijuana as an effective treatment for any psychiatric illness. Several studies have shown that cannabis use may in fact exacerbate or hasten the onset of psychiatric illnesses, as evidenced by both international trials and meta-analyses. This includes the contribution of marijuana to symptoms of mood disorders, anxiety and psychosis, particularly in young adulthood. Cannabis use is associated with the emergence of mood disorders, particularly symptoms of bipolar disorder, among those with a family history of mood disorder. Among those with major depressive disorder, co-morbid cannabis use is associated with increased rates of both suicidal ideation and attempts, raising grave safety concerns. Among those with a predisposition to psychotic disorders, cannabis may hasten the emergence of both positive and negative psychotic symptoms. The use of higher potency cannabis, for longer periods of time and with more frequency, is also associated with increased risk of psychosis.

Several studies have demonstrated the link between marijuana use and mood, anxiety and psychotic disorders among adolescents. Cannabis use is associated with increased depression, suicidal ideation, use of other substances and risky behavior among adolescents. Regular adolescent cannabis use is also associated with increased incidence of anxiety disorders. Cannabis use significantly increases the risk of psychotic disorders

among young adults. Additionally, younger age of cannabis use is associated with an earlier onset of psychosis among those at risk. Adolescents with a history of cannabis use tend to have higher severity of illness, lower psychosocial functioning, less insight, and longer courses of untreated psychosis compared to those without a history of cannabis use. These findings are of particular concern as symptoms often persist into adulthood, and therefore cannabis use may increase the risk of lifelong symptoms and disability due to mental illness. (see attachment)

While there exist the future possibility that certain varieties of cannabis, administered at certain predictable dosages and schedules will be proven to benefit certain mental health conditions while avoiding the risks of toxicity or withdrawal symptoms, this is not yet the case. As with any potent psychotropic drug, unpredictable composition and strengths will inevitably lead to inconsistent effects with problems from excessive dose (i.e. intoxication) and inadequate dose (withdrawal).

In my medical opinion, the one area of expanded indication for medical cannabis, where the benefits are likely to outweigh the risks, would be as an alternative to the management of chronic pain with harmful and ineffective opioids.

There are several other Medical Marijuana bills that have been scheduled for hearing (SB1159, SB173, SB716, SB319, SB970), indicating that expanding access to high-potency cannabis has a higher priority for the legislature, than doing the work necessary to ensure that health plan members have access to the safe and effective medical care they are paying for and are legally entitled to. With all the oversight and attention being paid to expanded use of high potency cannabis, a marginal issue for most people, why has there been so little legislative oversight of the health plan provider networks that nearly all of our people depend on for access to proven care?

Most worrisome is the foreseeable worsening of the shortage of psychiatric physicians likely due to this bill. By expanding the numbers of individuals with qualifying diagnoses, particularly to those most vulnerable to adverse effects of high-potency medical cannabis, SB174 would predictably increase the burden of mental illness on Hawaii's

health system. In addition to the triggering of episodes of Anxiety, Depression, Mania or Psychosis, the likelihood of toxicity from excessive dosing or of withdrawal from reduced dose will add to the burden on our strained mental health system. This is the opposite of the preventive approach needed to reduce unnecessary demands on our healthcare system. From the perspective of consumer protection and public health, this makes no sense.

Please, committee members, defer SB174, or amend qualifying conditions to include treatment for chronic pain and to remove the list of mental health problems it is known to cause or worsen (autism, anxiety, depression, insomnia, and stress).

Thank you for allowing me to testify on SB174, and your consideration of these concerns is appreciated.

Sincerely,

A handwritten signature in cursive script that reads "D. Douglas Smith".

D. Douglas Smith, M.D.

Position Statement on Marijuana as Medicine

Approved by the Board of Trustees, December 2013
Approved by the Assembly, November 2013

"Policy documents are approved by the APA Assembly and Board of Trustees...These are...position statements that define APA official policy on specific subjects..." – *APA Operations Manual*.

- There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development.
- Further research on the use of cannabis-derived substances as medicine should be encouraged and facilitated by the federal government. The adverse effects of marijuana, including, but not limited to, the likelihood of addiction, must be simultaneously studied.
- Policy and practice surrounding cannabis-derived substances should not be altered until sufficient clinical evidence supports such changes.
- If scientific evidence supports the use of cannabis-derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA.

Regarding state initiatives to authorize the use of marijuana for medical purposes:

- Medical treatment should be evidence-based and determined by professional standards of care; it should not be authorized by ballot initiatives.
- No medication approved by the FDA is smoked. Marijuana that is dispensed under a state-authorized program is not a specific product with controlled dosages. The buyer has no way of knowing the strength or purity of the product, as cannabis lacks the quality control of FDA-approved medicines.
- Prescribers and patients should be aware that the dosage administered by smoking is related to the depth and duration of the inhalation, and therefore difficult to standardize. The content and potency of various cannabinoids contained in marijuana can also vary, making dose standardization a challenging task.
- Physicians who recommend use of smoked marijuana for "medical" purposes should be fully aware of the risks and liabilities inherent in doing so.

AUTHORS:

Tauheed Zaman, M.D.
Richard N. Rosenthal, M.D.
John A. Renner, Jr., M.D.
Herbert D. Kleber, M.D.
Robert Milin, M.D.

See the related APA resource document [HERE](#).

Resource Document on Marijuana as Medicine

Approved by the Joint Reference Committee, October 2013

The findings, opinions, and conclusions of this report do not necessarily represent the views of the officers, trustees, or all members of the American Psychiatric Association. Views expressed are those of the authors." -- *APA Operations Manual*.

Tauheed Zaman, M.D.
Richard N. Rosenthal, M.D.
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Abstract

The medical use of marijuana has received considerable attention as several states have voted to remove civil and criminal penalties for patients with qualifying conditions. Yet, on a national level, marijuana remains a schedule I substance under the Controlled Substances Act (CSA), the most restrictive schedule enforced by the Drug Enforcement Administration (DEA) (1). The Food and Drug Administration (FDA), responsible for approving treatments after appropriate and rigorous study, additionally does not support the use of marijuana for medical purposes. This juxtaposition of practice and policy has prompted many professional medical organizations to issue official positions on the topic. This statement reflects the position of the American Psychiatric Association (APA) on the use of marijuana for psychiatric indications. It does not cover the use of synthetic cannabis-derived medications such as Dronabinol (Marinol), which has been studied and approved by the FDA for specific indications.

Medical Indications for Marijuana as Medicine

Much of the evidence supporting marijuana use for non-psychiatric medical diagnoses remains anecdotal. The indications with the most evidence include: severe nausea and vomiting associated with cancer chemotherapy (2), cachexia associated with Acquired Immune Deficiency Syndrome (AIDS) (3), spasticity secondary to neurological diseases such as muscular sclerosis (4), management of neuropathic pain (5), and rheumatoid arthritis (6). Several medical organizations have issued statements regarding indications for marijuana as medicine based on scientific evidence.

Contribution of Marijuana to Psychiatric Illness

There is currently no scientific evidence to support the use of marijuana as an effective treatment for any psychiatric illness. Several studies have shown that cannabis use may in fact exacerbate or hasten the onset of psychiatric illnesses, as evidenced by both international trials and meta-analyses (7-9). This includes the contribution of marijuana to symptoms of mood disorders, anxiety and psychosis, particularly in young adulthood^{10, 11}. Cannabis use is associated with the emergence of mood disorders,

particularly symptoms of bipolar disorder, among those with a family history of mood disorder (12). Among those with major depressive disorder, co-morbid cannabis use is associated with increased rates of both suicidal ideation and attempts, raising grave safety concerns (13). Among those with a predisposition to psychotic disorders, cannabis may hasten the emergence of both positive and negative psychotic symptoms (14). The use of higher potency cannabis, for longer periods of time and with more frequency, is also associated with increased risk of psychosis (15).

Several studies have demonstrated the link between marijuana use and mood, anxiety and psychotic disorders among adolescents. Cannabis use is associated with increased depression, suicidal ideation, use of other substances and risky behavior among adolescents¹⁶. Regular adolescent cannabis use is also associated with increased incidence of anxiety disorders (17). Cannabis use significantly increases the risk of psychotic disorders among young adults (18). Additionally, younger age of cannabis use is associated with an earlier onset of psychosis among those at risk (19). Adolescents with a history of cannabis use tend to have higher severity of illness, lower psychosocial functioning, less insight, and longer courses of untreated psychosis compared to those without a history of cannabis use²⁰. These findings are of particular concern as symptoms often persist into adulthood, and therefore cannabis use may increase the risk of lifelong symptoms and disability due to mental illness.

Serious Adverse Effects of Marijuana Use

Cognitive and Functional

Marijuana use is associated with serious cognitive problems such as short-term memory deficits, poor concentration, attention, and information processing (21). These impairments might be caused by neurotoxic effects of cannabis on the developing brain, the effects of which can lead to long-term cognitive problems well into adulthood (22, 23). Adolescents with daily cannabis use show deficits in learning up to six weeks after stopping marijuana use (24). This may contribute to significantly decreased academic achievement, including increased rates of school dropout, failure to enter higher education or attain higher degrees (25). Among both adolescents and adults, cannabis significantly impairs driving, particularly as the drug affects automatic driving functions in a highly dose-dependent fashion (26). Cannabis use, particularly in combination with alcohol, greatly increases the risk of motor vehicle crashes due to effects on cognition and coordination (27). Addiction and burden of psychiatric illness:

Cannabis use is associated with an increased risk of developing a cannabis use disorder. Studies indicate that 9% of users become dependent on cannabis, and this number increases to 25-50% among daily users and to 1 in 6 among adolescents (28). Adolescents remain at particular risk for cannabis use disorder, and can experience significant withdrawal symptoms including appetite changes, restlessness, irritability, depression, twitches and shakes, perspiration, and thoughts/cravings of cannabis (29). Marijuana use is also associated with poorer outcomes among those with mental illness. Among individuals with schizophrenia, cannabis use is associated with poorer long-term clinical outcomes (30). Individuals with psychotic illness may be more sensitive to both the psychosis-inducing and mood-altering effects of cannabis (31). This may explain why even among those taking medications for psychotic disorders, cannabis use is associated with an increased risk of relapse into psychotic symptoms (32).

Legalization of medical marijuana may reduce the perceived risks of use, the perception of societal disapproval, or the barriers to access, and potentially increase the incidence of the adverse events noted above.

Summary

Given the gravity of concerns regarding marijuana as medicine, professionals in both neurology and psychiatry have emphasized the importance of prospective studies to understand the mechanisms by which cannabis functions, and its impact on mental health and behavior before instituting changes in practice and policy (33, 34).

Organizations with Position Statements on Marijuana as Medicine as of April 2013

- American Academy of Child and Adolescent Psychiatry (AACAP)
- American Academy of Pediatrics (AAP)
- American Medical Association (AMA)
- American Society of Addiction Medicine (ASAM)
- American Cancer Society
- National Multiple Sclerosis Society

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To: Committee on Commerce, Consumer Protection, and Health
Senator Rosalyn Baker, Chair
Senator Clarence Nishihara, Vice Chair

Re: SB174 – Relating to Marijuana

Hearing: Wednesday, February 8, 2017, 9:00 am, Room 229

From: Clifton Otto, MD

Position: Support

Please consider also adding Amyotrophic Lateral Sclerosis (ALS) to this list of debilitating conditions.

Stress can certainly lead to worsening of symptoms in Autism, Anxiety, Depression, Epilepsy, Insomnia, Lupus, and Multiple Sclerosis, but may be difficult to justify as a stand-alone qualifying condition.

Please don't give in to the myth that only FDA approval justifies medical use. The intent of our Medical Use of Marijuana Program is to reduce the suffering of our patients by respecting the right of patients to choose the type of medical treatment that works best for them. Tens of thousands of patient years of use in Hawaii have already shown that marijuana is safe for medical use under supervision of a healthcare professional.

Thank you.

From: mailinglist@capitol.hawaii.gov
Sent: Monday, February 6, 2017 5:35 PM
To: CPH Testimony
Cc: naturadoc@gmail.com
Subject: Submitted testimony for SB174 on Feb 8, 2017 09:00AM

SB174

Submitted on: 2/6/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Bonnie Marsh	Individual	Support	No

Comments: Please support to include a wider ranger of medical conditions to qualify for a medical permit. Mahalo

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

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From: mailinglist@capitol.hawaii.gov
Sent: Monday, February 6, 2017 1:09 PM
To: CPH Testimony
Cc: wao-hsl@WeAreOne.cc
Subject: *Submitted testimony for SB174 on Feb 8, 2017 09:00AM*

SB174

Submitted on: 2/6/2017

Testimony for CPH on Feb 8, 2017 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Joseph Kohn MD	Individual	Support	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

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



Medical Cannabis Registry

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 Zip Code

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.

Anxiety

(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.

This petition includes new scientific research supporting the request to add "Anxiety" as a qualifying condition that was not present in the "General Anxiety Disorder" petition. This petition should be reviewed and not rejected for its similarity to an earlier petition due to the new evidence published by the Minnesota Department of Health, the Massachusetts Department of Health and other peer-reviewed medical research attached and included.

<https://www.mass.gov/report/massachusetts-department-of-public-health-marijuana-research>
(REF #77) <https://www.mass.gov/files/documents/2019/07/09/MBHS-full-report-final.pdf>
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 mood and or mental health 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.

In the 1999 National Academy of Sciences Institute of Medicine report on marijuana, the National Academy of Science found that thorough medical research shows that marijuana reduces anxiety for "many people".

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

(REF #99) <https://www.nap.edu/download/6376>

page 165

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.**

In a study of medical marijuana patients in Arizona, many patients reported significant relief levels of anxiety.

(REF #13) <https://www.ncbi.nlm.nih.gov/pubmed/26317379>

367 medical marijuana patients in Arizona were surveyed.

181 patients reported using medical marijuana to experience relief from Anxiety

General relief from Anxiety symptoms was 82.9% with medical marijuana,

Relief by medical marijuana compared to other medications was 79.3% for Anxiety

Less frequent use of other medications was 85.9% for Anxiety

Patients who suffer from Post Traumatic Stress Disorder find relief of anxiety with medical cannabis. PTSD is a

qualifying condition in Hawaii and other states. It makes logical sense to allow people who do not have PTSD to gain relief of anxiety by adding anxiety to the list of qualifying conditions.

In a small percentage of people, medical cannabis can aggravate their anxiety. For the majority of people, cannabis reduces anxiety. This contraindication is similar to other anti-anxiety prescriptions, for whom a small percentage, their anxiety can be aggravated. This is not a reason to reject a qualifying condition, merely a reality of using any medication. Some epilepsy medicines make seizures worse or more frequent.

Marijuana is safer than all prescription medications and most of OTC medications. Cannabis has less side effects, and no severe, toxic or dangerous side effects compared to all of the prescription medications used to treat Anxiety.

<https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml>

For example Benzodiazepines commonly used as anti anxiety medications, are responsible for hundreds of deaths each year in the United States.

<https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>

<https://directorsblog.nih.gov/2014/04/10/anxiety-reduction-exploring-the-role-of-cannabinoid-receptors/>

Relief of anxiety and stress is one of the most common reasons that people give for using marijuana

Anti-Anxiety medication Ativan may be implicated in Soundgarden's lead singer Chris Cornell's suicide.

<http://www.rollingstone.com/culture/news/ativan-what-you-need-to-know-about-anxiety-pills-w483638>

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 #98) <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.

The Mayo Clinic website has assembled dosage information on Medical Marijuana.

<http://www.mayoclinic.org/drugs-supplements/marijuana/dosing/hrb-20059701>

In the latest petition to add Anxiety to Ohio's medical marijuana program, the New Jersey Department of Health's final decision on a petition to add anxiety in New Jersey was included.

(REF 96) [https://med.ohio.gov/Portals/0/Publications/Medical%20Marijuana%20Petitions%202019/0133%20-%20Anxiety%20\[Rosenberger\].pdf?ver=2020-01-28-104750-247](https://med.ohio.gov/Portals/0/Publications/Medical%20Marijuana%20Petitions%202019/0133%20-%20Anxiety%20[Rosenberger].pdf?ver=2020-01-28-104750-247)

(REF 97)

https://www.nj.gov/health/medicalmarijuana/documents/agency_decision_letters/MMP_FAD_conditions_012319.pdf

New Jersey's medical cannabis program is similar to Hawaii's medical cannabis program. With similar requirements for petitions to meet.

On July 5, 2016, the Department published the Request for Petitions in the New Jersey Register advising

that from August 1, 2016 to August 31, 2016, it was accepting petitions to establish additional medical conditions as "debilitating" under the MMP. 43 NJR. 1395(a). The Request for Petitions stated that the Department was seeking petitions in accordance with the Act, which authorizes the Department to include additional debilitating medical conditions under the MMP.

In the Request for Petitions, the public was advised that submitted petitions were required to include the following information, pursuant to N.J.A.C. 8:64-53:

- (1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;
- (2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;
- (3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting, or otherwise severely impair the patient's ability to carry on activities of daily living;
- (4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;
- (5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and
- (6) Letters of support from physicians or other licensed health care professionals knowledgeable about the condition.

New Jersey found that Anxiety met the requirements and accepted Anxiety as a qualifying condition.

Anxiety

Based upon my independent review of the petitions, I am granting those seeking to add anxiety to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that anxiety satisfies this criteria.

Specifically, the American Psychiatric Association defines anxiety and anxiety disorders as conditions characterized by excessive fear and behavioral disturbances. Anxiety results from anticipation of a future threat and may be associated with symptoms of muscle tension, vigilance in preparation for future danger, and overly cautious or avoidant behaviors. Additionally, there are multiple ICD-10-CM codes for anxiety disorders. Because anxiety maintains a common definition in the medical community and has ICD-10-CM codes, I find that anxiety is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. From my review of this condition, the generally accepted treatments for anxiety are dependent on the symptoms and the severity of the particular disorder.

Mild and moderate forms of anxiety may not require a pharmacologic intervention, but may necessitate other

forms of treatment, such as meditation, mindfulness, breathing techniques as well as psychotherapy (counseling) or cognitive therapy.” The most common classes of medications used to combat anxiety disorders are antidepressants, anti-anxiety drugs, and beta— blockers.⁴⁹ Antidepressants are safe and effective but they may be risky for children, teens, and young adults.⁵⁰ Antidepressants also come with a “black box” warning — the FDA’s strongest warning — advising that some people may have suicidal thoughts or make suicide attempts while taking the medication.⁵¹ The most common anti-anxiety medications are called benzodiazepines.

As noted by the Panel, the common side effects of benzodiazepines include headache, confusion, tiredness, and in some cases nightmares and memory impairments.⁵² And, benzodiazepines carry a risk of dependence and addiction.⁵³ Furthermore, the FDA notes that the number of patients who were prescribed both an opioid analgesic and benzodiazepine increased by 41% between 2002 and 2014.⁵⁴ As a result, the FDA requires black box warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines to inform the patient about the serious risks associated with using these medications at the same time.⁵⁵ Thus, I find that the treatments for anxiety are recognized and accepted by the medical community as the treatments for this condition and relate to the suffering of the patient.

As for the third factor, which is whether the condition itself and for the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient’s ability to carry on activities of daily living, I find that both the anxiety condition itself as well as the treatments for this condition cause severe suffering for patients. Specifically, anxiety may lead to problems that negatively impact an individual’s activities of daily living and quality of life and may lead to suicide and depression. Anxiety disorders can also cause significant distress or interfere with social, occupational, and other areas of functioning. In fact, an estimated 31.1% of US. adults experience an anxiety disorder at some time in their lives.⁵⁶ Medications, in some instances, may exacerbate the symptoms and are associated with debilitating side effects that can prevent a patient from engaging in activities of daily living, thereby diminishing one’s quality of life. Accordingly, I find that both the condition of anxiety as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patients suffering caused by the condition and or the treatment thereof. As discussed above, mild and moderate forms of anxiety may be treated with meditation, mindfulness, breathing techniques as well as counseling or cognitive therapy that can be effective. Progression to medication therapy may be initiated; however, in both instances, one must consider the therapeutic response. Failure to respond to therapies or side effects associated with treatments may result in significant impacts on quality of life. As such, I find that there is an absence of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for migraine that cause suffering.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that cannabis is generally accepted as an effective treatment for anxiety.

The Panel discussed medical evidence that cannabis may exacerbate anxiety symptoms or that an effect related to cannabis may be associated with anxiety, such as dependence and cravings. Literature suggests that individuals with anxiety sensitivity may be more likely to turn to cannabis as a mechanism for coping with stress, which may in turn lead to problematic use behaviors.⁵⁷ However, the Panel further discussed a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, which found that there is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, which was assessed by a public speaking test utilizing individuals with social anxiety disorders.⁵⁸

On balance, the Panel recommended adding anxiety as an allowable condition under the MMP as research suggests that it could be helpful to some patients with this condition. I agree. While marijuana may not be effective for all anxiety sufferers, there is research evidencing that it may be helpful to some, especially those with social anxiety disorders. Thus, I find that there is acceptance in the medical community that marijuana is likely to relieve the suffering associated with some anxiety conditions. However, like any medical condition, the use of medical marijuana to treat anxiety must be explored by the medical professional treating the patient to determine whether it is the best and most appropriate course of treatment for the patient.

As for the final factor, which is whether there were letters from physicians or other licensed health care

professionals knowledgeable about the condition supporting the inclusion of anxiety under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of anxiety is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that anxiety should be added to the MMP.

In a previous qualifying condition petition for Generalized Anxiety Disorder, the Director of Health at the Hawaii Department of Health rejected adding the condition to the medical marijuana program. The main reason being that there is a lack of peer-reviewed scientific evidence showing beneficial use to treat GAD. This idea that peer-reviewed scientific evidence needs to conclusively show medical benefit or else no other qualifying conditions could be approved is wrong; due to the political nature of marijuana. Please allow me to explain.

The Hawaii medical cannabis law was created based on medical and anecdotal evidence. Anecdotal evidence was accepted because there is a lack of scientific research on the benefits of marijuana. Due to cannabis’s placement in schedule 1 of controlled substances in both state and federal laws. Quoting from the Hawaii Medical Cannabis Law:

https://www.capitol.hawaii.gov/session2000/acts/Act228_SB862_HD1_.htm

There is sufficient medical and **anecdotal evidence** to support the proposition that these diseases and conditions may respond favorably to a medically controlled use of marijuana.

This lack of research is due to the funding of marijuana research being regulated by NIDA, the National Institute of Drug Abuse. NIDA’s purpose is investigating the abuse potential of drugs, including cannabis, with focus solely on trying to prove the negatives of marijuana use. Since NIDA funds negative effects of marijuana research, research is granted on the flimsiest of theories and has corrupted and biased science. Forcing researchers to chase more NIDA grants for research to ensure they continue to have jobs.

Negative research findings are promoted wildly by NIDA when they are published. Even if the methodology of the study is flawed beyond belief. Even when other researchers try to duplicate the results and fail, NIDA continues to promote the flawed study as though it still has merit. An example of this can be found on NIDA's website

<https://www.drugabuse.gov/news-events/nida-notes/2016/08/study-questions-role-marijuana-in-teen-users-iq-decline>

This finding suggests that the twins’ IQ was affected by factors that twins share in their genes or family background, rather than factors in which they differed (e.g., drug use). A further analysis, comparing the impact of marijuana use on fraternal versus identical twins, suggested that family-wide environmental influences are more decisive than genes for determining IQ trajectory.

NIDA, without any evidence to back up the statement, goes on:

These findings contrast but are not entirely inconsistent with those of an earlier study that linked teen-onset regular marijuana use to IQ deficits in the fourth decade of life (see Early-Onset, Regular Cannabis Use Is Linked to IQ Decline). The researchers say that although their evidence indicates that marijuana exposure does not cause persistent loss of intellectual function up to age 20, **prolonged regular exposure for decades might do so.**

NIDA contradicts itself often, and continues to promote failed theories that bear no relationship to reality. Especially trying to say that marijuana is a gateway drug.

<https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-gateway-drug>

These findings are consistent with the idea of marijuana as a "gateway drug." However, the majority of people who use marijuana do not go on to use other, "harder" substances.

A more sinister theory promoted by NIDA, the DEA, and even physicians is that marijuana use increases the risk of Schizophrenia. This is so unbelievable that it is a slap in the face of science. Simply looking at reality, the larger numbers of people using, or admitting to use of marijuana, the large number of registered medical cannabis patients in the USA (roughly 1,000,000 to 2,000,000) and the flat schizophrenia rates as reported by the NIH and WHO completely invalidate all peer-reviewed published research on the topic of marijuana causing schizophrenia.

<https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml>

<https://www.who.int/news-room/fact-sheets/detail/schizophrenia>

In fact, a percentage of people diagnosed with schizophrenia use marijuana to reduce anxiety and help with symptoms. People with more severe schizophrenia use more marijuana, this is the basis for the theory that marijuana causes more severe symptoms of schizophrenia. Similar thinking is used against patients who have more severe pain, that marijuana somehow makes pain worse for patients and they have to use more marijuana to gain pain relief. Instead of the observable theory that people with more severe pain use more marijuana to treat their more severe pain than people who have less severe pain. No one makes the theory that aspirin makes pain worse, because people with more pain use more aspirin. Bad science.

The whole point of a state medical marijuana law is that the federal government has engineered a catch-22 circular logic loop about marijuana. States, mostly via people's ballot initiatives have sideswiped the FDA in approving a medicine. This is because the FDA has adopted a policy of only endorsing and approving of monotherapies, e.g. one or two isolated and specific chemicals per approved medicine. There is another policy to reject crude botanical medicines due to variations from plant to plant. These comments by the FDA are found in the DEA response to a petition to reschedule marijuana to schedule 2 and in congressional testimony. Even if a company submitted an IND to the FDA to study marijuana for the treatment of a disease, it would be rejected by the FDA on both of those policies.

The catch-22 comes when patients, nurses, physicians, governors, senators and representatives suggest that marijuana be investigated as a medicine. In congressional testimony, the FDA says we need more research before endorsing that. NIDA says we need more research before utilizing marijuana as a medicine. The DEA says we need more research before marijuana could be considered a medicine. So, if everyone agrees we need more research, where exactly is the research?

Individual physicians have attempted to research the benefits of marijuana within universities. What happens is that, at every turn, approval to study is blocked, delayed and rejected. See for example the 10 years of trying to study medical marijuana for treatment of PTSD in veterans.

<https://www.stripes.com/marijuana-ptsd-study-concludes-after-10-years-of-planning-research-1.570986>

Sisley and her team had to gain approval and support from the U.S. Food and Drug Administration, the Drug Enforcement Administration and the National Institute on Drug Abuse to initiate the research – a process that lasted years.

One study took several years just to begin. After NIDA provided marijuana for research that was full of seeds, stems and mold.

<https://health.hawaii.gov/medicalcannabisregistry/files/2017/08/Generalized-Anxiety-Disorder-08.09.17-Redacted.pdf>

The GAD petition submitted in 2017 included anecdotal evidence, peer-reviewed patient surveys, marijuana use reports and other information. It was rejected by the director due to not having enough peer-reviewed scientific research. One reason given for the rejection was that there was "no specific evidence to GAD". This is why exact specific conditions and waiting for peer-reviewed medical research will never work as an administrative rule for reviewing qualifying condition petitions. There will never be medical marijuana research that specifically mentions each of the hundreds of conditions that include anxiety as a symptom. Research studies are done with one drug and one condition. A rejection for not having a specific condition mentioned seems more like a pedantic nitpick and less like a legitimate reason when both GAD and anxiety share anxiety as the core symptom.

This GAD petition rejection uses the same reason the federal government does not approve of medical marijuana. If this requirement barrier of peer-reviewed research was erected, no state would have a medical marijuana program. Due to the federal policies which are a de facto prohibition on research for medical marijuana benefits. These state medical marijuana programs were created because the federal government failed to do research, and continues to prohibit new research. While the reality is that cannabis is a non toxic medicine, has always been a medicine and always will be a medicine.

Anxiety was also included with a bill in the Hawaii legislature to add qualifying conditions. The Department of Health testified, and in opposing the bill, the DOH stated it would rather include conditions via the petition process. The HDOH also gave another reason, that the dept wanted to delay adding the condition until dispensaries were active. Try naming another medication that is delayed and kept illegal because the department was waiting for a pharmacy to open. The

DOH needs to stop these petty games played with sick people's lives, rights and freedoms.

(REF #95) https://www.capitol.hawaii.gov/session2018/testimony/SB174_TESTIMONY_CPH_02-08-17.pdf

This is another wrong-headed approach to the process, and ignores why and what the medical marijuana law does. Allow me to explain the purpose of the law and the role of the DOH in it.

From the Hawaii medical cannabis law:

The legislature is aware of the legal problems associated with the legal acquisition of marijuana for medical use. However, the legislature believes that medical scientific evidence on the medicinal benefits of marijuana should be recognized.

...

Therefore, the purpose of this Act is to ensure that seriously ill people are not penalized by the State for the use of marijuana for strictly medical purposes when the patient's treating physician provides a professional opinion that the benefits of medical use of marijuana would likely outweigh the health risks for the qualifying patient.

The whole point of the medical marijuana program is not to endorse, nor recommend medical marijuana to patients. The purpose of the law is to NOT PENALIZE patients using medical marijuana with recommendations from their physicians. To protect patients from the laws prohibiting the use of marijuana.

Said another way, it is not the Department of Health's role to become the FDA and research medical marijuana. It is not the DOH's role to judge if medical marijuana is a medicine or not. It is not the DOH's role to decide which conditions marijuana is beneficial for either. That role is solely for a patient to decide if medical marijuana works for their conditions or not. Physicians have a role to make sure the patient's health is first priority over any medication.

The DOH's only role in the petition process is to protect medical marijuana patients from arrest.

People are currently illegally using marijuana to treat their conditions, specifically anxiety. The DOH has the power to protect these patients by adding qualifying conditions. Instead, the DOH has assumed the role of the FDA, denying petitions and opposing adding conditions legislatively. Waiting for peer-reviewed medical evidence that by all accounts is not coming within the next two decades.

This delay and denial of the reality of medical marijuana patients conditions needs to stop.

- (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.

Anxiety is a recognized medical condition affecting millions of Americans each year.

<https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml>

The wide variety of anxiety disorders differ by the objects or situations that induce them, but share features of excessive anxiety and related behavioral disturbances. Anxiety disorders can interfere with daily activities such as job performance, school work, and relationships.

Based on diagnostic interview data from the National Comorbidity Study Replication (NCS-R), Figure 1 shows past year prevalence of any anxiety disorder among U.S. adults aged 18 or older.¹

An estimated 19.1% of U.S. adults had any anxiety disorder in the past year.

Past year prevalence of any anxiety disorder was higher for females (23.4%) than for males (14.3%).

An estimated 31.1% of U.S. adults experience any anxiety disorder at some time in their lives.

Anxiety affects a large portion of the people in the United States, costing billions of dollars in medical treatment costs.

<https://www.cdc.gov/mentalhealth/basics/burden.htm>

Anxiety:

- Anxiety disorders, which include panic disorder, generalized anxiety disorder, post-traumatic stress disorder, phobias, and separation anxiety disorder, are the most common class of mental disorders present in the general population.
 - The estimated lifetime prevalence of any anxiety disorder is over 15%, while the 12-month prevalence is more than 10%.
 - Prevalence estimates of anxiety disorders are generally higher in developed countries than in developing countries.
 - Most anxiety disorders are more prevalent in women than in men.
- One study estimated the annual cost of anxiety disorders in the United States to be approximately \$42.3 billion in the 1990s, a majority of which was due to non-psychiatric medical treatment costs. This estimate focused on short-term effects and did not include the effect of outcomes such as the increased risk of other disorders.

(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.

Anxiety can cause a person to withdrawal from talking to other people or even going outside. Anxiety can diminish or completely debilitate a person from interviewing for a job, making day to day decisions, making personal relationships or thriving.

Instead of dealing and treating anxiety, the world instead decided to call anxiety being an introvert. An "introvert" is a "shy, reticent person". In other words, a person who has so much anxiety that they would rather hide than speak to someone else. Shyness is anxiety.

<https://www.nimh.nih.gov/health/publications/social-anxiety-disorder-more-than-just-shyness/index.shtml>

The reason this petition is for "Anxiety" and not "social anxiety disorder" is because each year there seems to be a new disorder with the core symptom being anxiety. Panic Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, PTSD. Anxiety is the common condition.

<https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml>

Any Anxiety Disorder with Impairment Among Adults

Of adults with any anxiety disorder in the past year, degree of impairment ranged from mild to severe, as shown in Figure 2. Impairment was determined by scores on the Sheehan Disability Scale.

Among adults with any anxiety disorder, an estimated 22.8% had serious impairment, and 33.7% had moderate impairment.¹

A majority of people with any anxiety disorder experienced mild impairment (43.5%).¹

1. Harvard Medical School, 2007. National Comorbidity Survey (NCS). (2017, August 21). Retrieved from <https://www.hcp.med.harvard.edu/ncs/index.php>. Data Table 2: 12-month prevalence DSM-IV/WMH-CIDI disorders by sex and cohort.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC181171/>

Although the principal symptoms of anxiety disorders include fear, excessive worry, nervousness, and obsessions, a multitude of physical symptoms also may be present. These somatic symptoms—which include heart palpitations, gastrointestinal problems, sweating, fainting, and chronic pain—can confound the diagnosis and resist all forms of medical management, unless the underlying anxiety source is identified and treated. Delays in diagnosis and treatment can be expensive for the patient, physician, and society: unnecessary tests and ineffective treatments increase medical costs, and **anxiety symptoms may lead to loss of income and productivity, financial dependence, and even suicide.**

(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.

N/A

(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.

(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.

Selected quotes and transcribed tables are taken from the following research and presented below.

1. <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.

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%).

3. <https://doi.org/10.1016/j.jpain.2007.09.002>

A randomized, double-blind, placebo-controlled trial was conducted to determine the benefit of nabilone in pain management and quality of life improvement in 40 patients with fibromyalgia.

There were significant decreases in the VAS, FIQ, and anxiety in the nabilone treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks, respectively. Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with

significant benefits in pain relief and functional improvement.

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

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.

5. <https://doi.org/10.1080/02791072.2011.587700>

Of 1,746 patients, 37.8% self-reported therapeutic benefits from medical marijuana for anxiety.

16.9% of patients self-reported therapeutic benefits from medical marijuana for panic attacks.

6. <https://www.ncbi.nlm.nih.gov/pubmed/6117575>

The results of the study showed a dramatic improvement in anxiety in the nabilone group when compared with placebo (P less than 0.001). Side effects reported were dry mouth, dry eyes, and drowsiness. Patients did not report any of the subjective "altered state" experience of marijuana.

7. <https://www.ncbi.nlm.nih.gov/pubmed/15857739>

Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), **anxiety (93%)**, nerve pain (90%), depression (86%), and paresthesia (85%).

8. <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.

9. <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.

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

Of 21 patients reporting stress, 20 said medical marijuana helped moderate-complete relief.

Of 16 patients reporting mood, all 16 said medical marijuana helped moderate-complete relief.

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

11. <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.

12. <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.

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

367 medical marijuana patients in Arizona were surveyed.
181 patients reported using medical marijuana to experience relief from Anxiety
164 patients reported using medical marijuana to experience relief from Stress.
General relief from Anxiety symptoms was 82.9% and 87.2% for Stress,

Relief by medical marijuana compared to other medications was 79.3% for Anxiety and 91.6 for Stress.

Less frequent use of other medications was 85.9% for Anxiety and 79.1% for Stress.

14. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3285527/>

One Hundred Canadian medical marijuana patients were surveyed in 2007-2008. 60.2% said they used medical marijuana to reduce anxiety.

15. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1262744/>

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.

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.

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%).

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 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 . 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%).

16. <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.

17. <https://doi.org/10.1111/dar.12323>

Participants presented with the range of conditions that is generally consistent with surveys of CTP users, the most prominent conditions being pain (32%), mood (i.e. anxiety and depression (18%), arthritis (15%), HIV (10%), gastrointestinal disorder (7%)

18. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5422566/>

We previously reported in an earlier survey that of 1,429 respondents, 61% reported using cannabis for managing pain, 58% reported using cannabis for anxiety and 50% reported using cannabis for depression. In the current analysis, these same conditions were also the most commonly reported conditions by respondents. Of the 1,040 participants reporting pain and/or intractable pain, 619 (59.52%) reported depression and anxiety as comorbidities. As such, the odds of reporting substituting cannabis for prescription drugs were more than one and a half times greater (OR, 1.66; 95% CI,

1.27–2.16) among those reporting using it to manage pain, anxiety and depression than among those using it to manage only one of the three conditions.

This team previously reported that in a survey of 1,429 medical cannabis users, 61% reported cannabis use for pain, 58% reported cannabis use for anxiety and 50% reported using cannabis to manage depression. In 2016, Dale and Stacey reported that those using cannabis for pain were more likely to be substituting for prescription drugs. In 2017, Walsh et al published a review of medical cannabis and mental health to try to better understand how medical cannabis use may impact areas of potential concern for clinicians. "Relaxation and relief of anxiety" and "relief of negative mood" or depression were among the most widely reported conditions in 60 publications included in their analysis. Because it is common for chronic pain patients to be prescribed combinatorial pharmacotherapy to address comorbidity with depression and/or anxiety, it is largely unknown how often patients may be discontinuing prescription medications when initiating cannabis use.

Taken with preclinical data on the role of the endocannabinoid system in stress, pain processing and immune homeostasis, it is clear that future investigation is warranted using controlled trials with human subjects to better understand the role that cannabis may play in treating pain, anxiety, depression and other conditions.

19. <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.

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

Of 628 Canadian medical marijuana patients:

463 patients reported using medical marijuana to treat anxiety.

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.

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.

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.

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

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]

22. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3691841/>

While the controversies surrounding cannabis are far from subdued (and are often permeated and masked by conflicting ideological credos), standardized studies on cannabinoids have highlighted that the psychological and behavioral outcomes of this substance are highly variable and range from relaxation, euthymia and heightened sociability to panic, paranoid ideation and psychosis [112 - 116]. A corollary of this observation is that the high comorbidity rate between cannabis use disorders and psychiatric conditions [100 - 105] may indicate that cannabis consumption is either a concurring cause or a “self-therapeutic” strategy for anxiety and mood disorders [117 - 123]. The latter interpretation is supported by the observation that anxiety-spectrum disturbances and traumas in early developmental stages are a strong predictor for later cannabis use disorders [124 - 127]; furthermore, several lines of evidence suggest that the anxiolytic effects of THC may partially account for the high prevalence of cannabis use in patients affected by PTSD [128 - 131] and OCD [132]. Accordingly, recent clinical studies have shown that THC elicits therapeutic effects in OCD [133] and trichotillomania, an impulse-control disorder characterized by compulsive hair-pulling [134].

23. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604171/>

Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

24. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604174/>

Although clinical studies in this area are difficult to do, even in countries where the use of cannabis has been allowed for years, there is a clear role for cannabis products in symptom management for these difficult conditions.

25. <https://www.ncbi.nlm.nih.gov/pubmed/22729452>

RESULTS:

Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder.

CONCLUSION:

Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

26. <https://doi.org/10.2202/1941-2851.1017>

1655 Patients reported using medical marijuana for these conditions:

Anxiety disorders 18.7% of patients

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.

27. <https://doi.org/10.1176/appi.ajp.2007.07061016>

Hence, it can be speculated that the anti-obsessive effect observed in our patients may have been a consequence of the glutamate modulation of the cannabinoid dronabinol.

28. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4349825/>

The findings from the study indicate that cannabis use is associated with a subsequent change in positive affect, depressive symptoms and manic symptoms over the course of daily life. No evidence for the use of cannabis to self-

medicate minor fluctuations in negative affect or BD symptoms was revealed. Participants in the study were currently well and out of episode. Future research should explore whether the self-medication hypothesis is more relevant to individuals that are in the acute stages of depression or mania. This would be consistent with the broader self-medication hypothesis in BD where individuals have reported finding cannabis useful in the management of their symptoms.

29. <https://www.ncbi.nlm.nih.gov/pubmed/9692379>

The authors present case histories indicating that a number of patients find cannabis (marihuana) useful in the treatment of their bipolar disorder. Some used it to treat mania, depression, or both. They stated that it was more effective than conventional drugs, or helped relieve the side effects of those drugs. One woman found that cannabis curbed her manic rages; she and her husband have worked to make it legally available as a medicine.

Others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects. Another case illustrates the fact that medical cannabis users are in danger of arrest, especially when children are encouraged to inform on parents by some drug prevention programs. An analogy is drawn between the status of cannabis today and that of lithium in the early 1950s, when its effect on mania had been discovered but there were no controlled studies. In the case of cannabis, the law has made such studies almost impossible, and the only available evidence is anecdotal. The potential for cannabis as a treatment for bipolar disorder unfortunately can not be fully explored in the present social circumstances.

30. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4898690/>

Findings suggest that for some bipolar patients, marijuana may result in partial alleviation of clinical symptoms. Moreover, this improvement is not at the expense of additional cognitive impairment.

31. <https://www.ncbi.nlm.nih.gov/pubmed/17703715>

Subjective reports by patients suggest an overall positive effect, but these may be unreliable. We herein report a case in which mood data was prospectively collected over two years of total substance abstinence and two years of extreme marijuana use. Marijuana use did not alter the total number of days of abnormal mood, however, marijuana was associated with an increase in the number of hypomanic days and a decrease in the number of depressed days. While not conclusive, the data suggest that marijuana may indeed have an effect on mood in bipolar patients that needs to be systematically examined.

32. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652027/>

Cannabis use diminishes some of the adverse effects of neurological and psychiatric disorders.

33. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4323143/>

These results suggest that cannabis use has clinical implications for the early course of BD (Bipolar Disorder) by increasing mood level.

34. <https://doi.org/10.1111/j.1368-5031.2005.00271.x>

Medicinal cannabis use was Reported by patients with chronic pain(25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (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 in the United States. 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 anxiety.

In its first year of reports, the Minnesota DOH published patient comments about the beneficial effects of the medical marijuana.

(REF #98) <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>

Many such comments are found within the above report.

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

<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 anxiety symptoms, and a large percentage of patients continue to maintain that reduction of anxiety for 4 months.

(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 which show a very small percentage of people experience a worsening of anxiety symptoms. I urge you to read them all as it shows how small the number of adverse anxiety 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

Although the comments mention anxiety as a side effect, sometimes it is not the cannabis's fault, but prohibition's fault, as this comment rated at score level 4 shows:

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!

Massachusetts published a report on its medical marijuana patients and their benefits.

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

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

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

mood and or mental health for a large percentage of people.

Page 10:

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.

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.

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

N/A



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



Medical Cannabis Registry

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 Zip Code

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.

Anxiety

(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.

This petition includes new scientific research supporting the request to add "Anxiety" as a qualifying condition that was not present in the "General Anxiety Disorder" petition. This petition should be reviewed and not rejected for its similarity to an earlier petition due to the new evidence published by the Minnesota Department of Health, the Massachusetts Department of Health and other peer-reviewed medical research attached and included.

<https://www.mass.gov/report/massachusetts-department-of-public-health-marijuana-research>
(REF #77) <https://www.mass.gov/files/documents/2019/07/09/MBHS-full-report-final.pdf>
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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.

In the 1999 National Academy of Sciences Institute of Medicine report on marijuana, the National Academy of Science found that thorough medical research shows that marijuana reduces anxiety for "many people".

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

(REF #99) <https://www.nap.edu/download/6376>

page 165

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.**

In a study of medical marijuana patients in Arizona, many patients reported significant relief levels of anxiety.

(REF #13) <https://www.ncbi.nlm.nih.gov/pubmed/26317379>

367 medical marijuana patients in Arizona were surveyed.

181 patients reported using medical marijuana to experience relief from Anxiety

General relief from Anxiety symptoms was 82.9% with medical marijuana,

Relief by medical marijuana compared to other medications was 79.3% for Anxiety

Less frequent use of other medications was 85.9% for Anxiety

Patients who suffer from Post Traumatic Stress Disorder find relief of anxiety with medical cannabis. PTSD is a

qualifying condition in Hawaii and other states. It makes logical sense to allow people who do not have PTSD to gain relief of anxiety by adding anxiety to the list of qualifying conditions.

In a small percentage of people, medical cannabis can aggravate their anxiety. For the majority of people, cannabis reduces anxiety. This contraindication is similar to other anti-anxiety prescriptions, for whom a small percentage, their anxiety can be aggravated. This is not a reason to reject a qualifying condition, merely a reality of using any medication. Some epilepsy medicines make seizures worse or more frequent.

Marijuana is safer than all prescription medications and most of OTC medications. Cannabis has less side effects, and no severe, toxic or dangerous side effects compared to all of the prescription medications used to treat Anxiety.

<https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml>

For example Benzodiazepines commonly used as anti anxiety medications, are responsible for hundreds of deaths each year in the United States.

<https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>

<https://directorsblog.nih.gov/2014/04/10/anxiety-reduction-exploring-the-role-of-cannabinoid-receptors/>

Relief of anxiety and stress is one of the most common reasons that people give for using marijuana

Anti-Anxiety medication Ativan may be implicated in Soundgarden's lead singer Chris Cornell's suicide.

<http://www.rollingstone.com/culture/news/ativan-what-you-need-to-know-about-anxiety-pills-w483638>

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 #98) <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.

The Mayo Clinic website has assembled dosage information on Medical Marijuana.

<http://www.mayoclinic.org/drugs-supplements/marijuana/dosing/hrb-20059701>

In the latest petition to add Anxiety to Ohio's medical marijuana program, the New Jersey Department of Health's final decision on a petition to add anxiety in New Jersey was included.

(REF 96) [https://med.ohio.gov/Portals/0/Publications/Medical%20Marijuana%20Petitions%202019/0133%20-%20Anxiety%20\[Rosenberger\].pdf?ver=2020-01-28-104750-247](https://med.ohio.gov/Portals/0/Publications/Medical%20Marijuana%20Petitions%202019/0133%20-%20Anxiety%20[Rosenberger].pdf?ver=2020-01-28-104750-247)

(REF 97)

https://www.nj.gov/health/medicalmarijuana/documents/agency_decision_letters/MMP_FAD_conditions_012319.pdf

New Jersey's medical cannabis program is similar to Hawaii's medical cannabis program. With similar requirements for petitions to meet.

On July 5, 2016, the Department published the Request for Petitions in the New Jersey Register advising

that from August 1, 2016 to August 31, 2016, it was accepting petitions to establish additional medical conditions as "debilitating" under the MMP. 43 NJR. 1395(a). The Request for Petitions stated that the Department was seeking petitions in accordance with the Act, which authorizes the Department to include additional debilitating medical conditions under the MMP.

In the Request for Petitions, the public was advised that submitted petitions were required to include the following information, pursuant to N.J.A.C. 8:64-53:

- (1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;
- (2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;
- (3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting, or otherwise severely impair the patient's ability to carry on activities of daily living;
- (4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;
- (5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and
- (6) Letters of support from physicians or other licensed health care professionals knowledgeable about the condition.

New Jersey found that Anxiety met the requirements and accepted Anxiety as a qualifying condition.

Anxiety

Based upon my independent review of the petitions, I am granting those seeking to add anxiety to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that anxiety satisfies this criteria.

Specifically, the American Psychiatric Association defines anxiety and anxiety disorders as conditions characterized by excessive fear and behavioral disturbances. Anxiety results from anticipation of a future threat and may be associated with symptoms of muscle tension, vigilance in preparation for future danger, and overly cautious or avoidant behaviors. Additionally, there are multiple ICD-10-CM codes for anxiety disorders. Because anxiety maintains a common definition in the medical community and has ICD-10-CM codes, I find that anxiety is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. From my review of this condition, the generally accepted treatments for anxiety are dependent on the symptoms and the severity of the particular disorder.

Mild and moderate forms of anxiety may not require a pharmacologic intervention, but may necessitate other

forms of treatment, such as meditation, mindfulness, breathing techniques as well as psychotherapy (counseling) or cognitive therapy.” The most common classes of medications used to combat anxiety disorders are antidepressants, anti-anxiety drugs, and beta— blockers.⁴⁹ Antidepressants are safe and effective but they may be risky for children, teens, and young adults.⁵⁰ Antidepressants also come with a “black box” warning — the FDA’s strongest warning — advising that some people may have suicidal thoughts or make suicide attempts while taking the medication.⁵¹ The most common anti-anxiety medications are called benzodiazepines.

As noted by the Panel, the common side effects of benzodiazepines include headache, confusion, tiredness, and in some cases nightmares and memory impairments.⁵² And, benzodiazepines carry a risk of dependence and addiction.⁵³ Furthermore, the FDA notes that the number of patients who were prescribed both an opioid analgesic and benzodiazepine increased by 41% between 2002 and 2014.⁵⁴ As a result, the FDA requires black box warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines to inform the patient about the serious risks associated with using these medications at the same time.⁵⁵ Thus, I find that the treatments for anxiety are recognized and accepted by the medical community as the treatments for this condition and relate to the suffering of the patient.

As for the third factor, which is whether the condition itself and for the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient’s ability to carry on activities of daily living, I find that both the anxiety condition itself as well as the treatments for this condition cause severe suffering for patients. Specifically, anxiety may lead to problems that negatively impact an individual’s activities of daily living and quality of life and may lead to suicide and depression. Anxiety disorders can also cause significant distress or interfere with social, occupational, and other areas of functioning. In fact, an estimated 31.1% of US. adults experience an anxiety disorder at some time in their lives.⁵⁶ Medications, in some instances, may exacerbate the symptoms and are associated with debilitating side effects that can prevent a patient from engaging in activities of daily living, thereby diminishing one’s quality of life. Accordingly, I find that both the condition of anxiety as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patients suffering caused by the condition and or the treatment thereof. As discussed above, mild and moderate forms of anxiety may be treated with meditation, mindfulness, breathing techniques as well as counseling or cognitive therapy that can be effective. Progression to medication therapy may be initiated; however, in both instances, one must consider the therapeutic response. Failure to respond to therapies or side effects associated with treatments may result in significant impacts on quality of life. As such, I find that there is an absence of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for migraine that cause suffering.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that cannabis is generally accepted as an effective treatment for anxiety.

The Panel discussed medical evidence that cannabis may exacerbate anxiety symptoms or that an effect related to cannabis may be associated with anxiety, such as dependence and cravings. Literature suggests that individuals with anxiety sensitivity may be more likely to turn to cannabis as a mechanism for coping with stress, which may in turn lead to problematic use behaviors.⁵⁷ However, the Panel further discussed a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, which found that there is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, which was assessed by a public speaking test utilizing individuals with social anxiety disorders.⁵⁸

On balance, the Panel recommended adding anxiety as an allowable condition under the MMP as research suggests that it could be helpful to some patients with this condition. I agree. While marijuana may not be effective for all anxiety sufferers, there is research evidencing that it may be helpful to some, especially those with social anxiety disorders. Thus, I find that there is acceptance in the medical community that marijuana is likely to relieve the suffering associated with some anxiety conditions. However, like any medical condition, the use of medical marijuana to treat anxiety must be explored by the medical professional treating the patient to determine whether it is the best and most appropriate course of treatment for the patient.

As for the final factor, which is whether there were letters from physicians or other licensed health care

professionals knowledgeable about the condition supporting the inclusion of anxiety under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of anxiety is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that anxiety should be added to the MMP.

In a previous qualifying condition petition for Generalized Anxiety Disorder, the Director of Health at the Hawaii Department of Health rejected adding the condition to the medical marijuana program. The main reason being that there is a lack of peer-reviewed scientific evidence showing beneficial use to treat GAD. This idea that peer-reviewed scientific evidence needs to conclusively show medical benefit or else no other qualifying conditions could be approved is wrong; due to the political nature of marijuana. Please allow me to explain.

The Hawaii medical cannabis law was created based on medical and anecdotal evidence. Anecdotal evidence was accepted because there is a lack of scientific research on the benefits of marijuana. Due to cannabis’s placement in schedule 1 of controlled substances in both state and federal laws. Quoting from the Hawaii Medical Cannabis Law:

https://www.capitol.hawaii.gov/session2000/acts/Act228_SB862_HD1_.htm

There is sufficient medical and **anecdotal evidence** to support the proposition that these diseases and conditions may respond favorably to a medically controlled use of marijuana.

This lack of research is due to the funding of marijuana research being regulated by NIDA, the National Institute of Drug Abuse. NIDA’s purpose is investigating the abuse potential of drugs, including cannabis, with focus solely on trying to prove the negatives of marijuana use. Since NIDA funds negative effects of marijuana research, research is granted on the flimsiest of theories and has corrupted and biased science. Forcing researchers to chase more NIDA grants for research to ensure they continue to have jobs.

Negative research findings are promoted wildly by NIDA when they are published. Even if the methodology of the study is flawed beyond belief. Even when other researchers try to duplicate the results and fail, NIDA continues to promote the flawed study as though it still has merit. An example of this can be found on NIDA's website

<https://www.drugabuse.gov/news-events/nida-notes/2016/08/study-questions-role-marijuana-in-teen-users-iq-decline>

This finding suggests that the twins’ IQ was affected by factors that twins share in their genes or family background, rather than factors in which they differed (e.g., drug use). A further analysis, comparing the impact of marijuana use on fraternal versus identical twins, suggested that family-wide environmental influences are more decisive than genes for determining IQ trajectory.

NIDA, without any evidence to back up the statement, goes on:

These findings contrast but are not entirely inconsistent with those of an earlier study that linked teen-onset regular marijuana use to IQ deficits in the fourth decade of life (see Early-Onset, Regular Cannabis Use Is Linked to IQ Decline). The researchers say that although their evidence indicates that marijuana exposure does not cause persistent loss of intellectual function up to age 20, **prolonged regular exposure for decades might do so.**

NIDA contradicts itself often, and continues to promote failed theories that bear no relationship to reality. Especially trying to say that marijuana is a gateway drug.

<https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-gateway-drug>

These findings are consistent with the idea of marijuana as a "gateway drug." However, the majority of people who use marijuana do not go on to use other, "harder" substances.

A more sinister theory promoted by NIDA, the DEA, and even physicians is that marijuana use increases the risk of Schizophrenia. This is so unbelievable that it is a slap in the face of science. Simply looking at reality, the larger numbers of people using, or admitting to use of marijuana, the large number of registered medical cannabis patients in the USA (roughly 1,000,000 to 2,000,000) and the flat schizophrenia rates as reported by the NIH and WHO completely invalidate all peer-reviewed published research on the topic of marijuana causing schizophrenia.

<https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml>

<https://www.who.int/news-room/fact-sheets/detail/schizophrenia>

In fact, a percentage of people diagnosed with schizophrenia use marijuana to reduce anxiety and help with symptoms. People with more severe schizophrenia use more marijuana, this is the basis for the theory that marijuana causes more severe symptoms of schizophrenia. Similar thinking is used against patients who have more severe pain, that marijuana somehow makes pain worse for patients and they have to use more marijuana to gain pain relief. Instead of the observable theory that people with more severe pain use more marijuana to treat their more severe pain than people who have less severe pain. No one makes the theory that aspirin makes pain worse, because people with more pain use more aspirin. Bad science.

The whole point of a state medical marijuana law is that the federal government has engineered a catch-22 circular logic loop about marijuana. States, mostly via people's ballot initiatives have sideswiped the FDA in approving a medicine. This is because the FDA has adopted a policy of only endorsing and approving of monotherapies, e.g. one or two isolated and specific chemicals per approved medicine. There is another policy to reject crude botanical medicines due to variations from plant to plant. These comments by the FDA are found in the DEA response to a petition to reschedule marijuana to schedule 2 and in congressional testimony. Even if a company submitted an IND to the FDA to study marijuana for the treatment of a disease, it would be rejected by the FDA on both of those policies.

The catch-22 comes when patients, nurses, physicians, governors, senators and representatives suggest that marijuana be investigated as a medicine. In congressional testimony, the FDA says we need more research before endorsing that. NIDA says we need more research before utilizing marijuana as a medicine. The DEA says we need more research before marijuana could be considered a medicine. So, if everyone agrees we need more research, where exactly is the research?

Individual physicians have attempted to research the benefits of marijuana within universities. What happens is that, at every turn, approval to study is blocked, delayed and rejected. See for example the 10 years of trying to study medical marijuana for treatment of PTSD in veterans.

<https://www.stripes.com/marijuana-ptsd-study-concludes-after-10-years-of-planning-research-1.570986>

Sisley and her team had to gain approval and support from the U.S. Food and Drug Administration, the Drug Enforcement Administration and the National Institute on Drug Abuse to initiate the research – a process that lasted years.

One study took several years just to begin. After NIDA provided marijuana for research that was full of seeds, stems and mold.

<https://health.hawaii.gov/medicalcannabisregistry/files/2017/08/Generalized-Anxiety-Disorder-08.09.17-Redacted.pdf>

The GAD petition submitted in 2017 included anecdotal evidence, peer-reviewed patient surveys, marijuana use reports and other information. It was rejected by the director due to not having enough peer-reviewed scientific research. One reason given for the rejection was that there was "no specific evidence to GAD". This is why exact specific conditions and waiting for peer-reviewed medical research will never work as an administrative rule for reviewing qualifying condition petitions. There will never be medical marijuana research that specifically mentions each of the hundreds of conditions that include anxiety as a symptom. Research studies are done with one drug and one condition. A rejection for not having a specific condition mentioned seems more like a pedantic nitpick and less like a legitimate reason when both GAD and anxiety share anxiety as the core symptom.

This GAD petition rejection uses the same reason the federal government does not approve of medical marijuana. If this requirement barrier of peer-reviewed research was erected, no state would have a medical marijuana program. Due to the federal policies which are a de facto prohibition on research for medical marijuana benefits. These state medical marijuana programs were created because the federal government failed to do research, and continues to prohibit new research. While the reality is that cannabis is a non toxic medicine, has always been a medicine and always will be a medicine.

Anxiety was also included with a bill in the Hawaii legislature to add qualifying conditions. The Department of Health testified, and in opposing the bill, the DOH stated it would rather include conditions via the petition process. The HDOH also gave another reason, that the dept wanted to delay adding the condition until dispensaries were active. Try naming another medication that is delayed and kept illegal because the department was waiting for a pharmacy to open. The

DOH needs to stop these petty games played with sick people's lives, rights and freedoms.

(REF #95) https://www.capitol.hawaii.gov/session2018/testimony/SB174_TESTIMONY_CPH_02-08-17.pdf

This is another wrong-headed approach to the process, and ignores why and what the medical marijuana law does. Allow me to explain the purpose of the law and the role of the DOH in it.

From the Hawaii medical cannabis law:

The legislature is aware of the legal problems associated with the legal acquisition of marijuana for medical use. However, the legislature believes that medical scientific evidence on the medicinal benefits of marijuana should be recognized.

...

Therefore, the purpose of this Act is to ensure that seriously ill people are not penalized by the State for the use of marijuana for strictly medical purposes when the patient's treating physician provides a professional opinion that the benefits of medical use of marijuana would likely outweigh the health risks for the qualifying patient.

The whole point of the medical marijuana program is not to endorse, nor recommend medical marijuana to patients. The purpose of the law is to NOT PENALIZE patients using medical marijuana with recommendations from their physicians. To protect patients from the laws prohibiting the use of marijuana.

Said another way, it is not the Department of Health's role to become the FDA and research medical marijuana. It is not the DOH's role to judge if medical marijuana is a medicine or not. It is not the DOH's role to decide which conditions marijuana is beneficial for either. That role is solely for a patient to decide if medical marijuana works for their conditions or not. Physicians have a role to make sure the patient's health is first priority over any medication.

The DOH's only role in the petition process is to protect medical marijuana patients from arrest.

People are currently illegally using marijuana to treat their conditions, specifically anxiety. The DOH has the power to protect these patients by adding qualifying conditions. Instead, the DOH has assumed the role of the FDA, denying petitions and opposing adding conditions legislatively. Waiting for peer-reviewed medical evidence that by all accounts is not coming within the next two decades.

This delay and denial of the reality of medical marijuana patients conditions needs to stop.

- (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.

Anxiety is a recognized medical condition affecting millions of Americans each year.

<https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml>

The wide variety of anxiety disorders differ by the objects or situations that induce them, but share features of excessive anxiety and related behavioral disturbances. Anxiety disorders can interfere with daily activities such as job performance, school work, and relationships.

Based on diagnostic interview data from the National Comorbidity Study Replication (NCS-R), Figure 1 shows past year prevalence of any anxiety disorder among U.S. adults aged 18 or older.¹

An estimated 19.1% of U.S. adults had any anxiety disorder in the past year.

Past year prevalence of any anxiety disorder was higher for females (23.4%) than for males (14.3%).

An estimated 31.1% of U.S. adults experience any anxiety disorder at some time in their lives.

Anxiety affects a large portion of the people in the United States, costing billions of dollars in medical treatment costs.

<https://www.cdc.gov/mentalhealth/basics/burden.htm>

Anxiety:

- Anxiety disorders, which include panic disorder, generalized anxiety disorder, post-traumatic stress disorder, phobias, and separation anxiety disorder, are the most common class of mental disorders present in the general population.
 - The estimated lifetime prevalence of any anxiety disorder is over 15%, while the 12-month prevalence is more than 10%.
 - Prevalence estimates of anxiety disorders are generally higher in developed countries than in developing countries.
 - Most anxiety disorders are more prevalent in women than in men.
- One study estimated the annual cost of anxiety disorders in the United States to be approximately \$42.3 billion in the 1990s, a majority of which was due to non-psychiatric medical treatment costs. This estimate focused on short-term effects and did not include the effect of outcomes such as the increased risk of other disorders.

(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.

Anxiety can cause a person to withdrawal from talking to other people or even going outside. Anxiety can diminish or completely debilitate a person from interviewing for a job, making day to day decisions, making personal relationships or thriving.

Instead of dealing and treating anxiety, the world instead decided to call anxiety being an introvert. An "introvert" is a "shy, reticent person". In other words, a person who has so much anxiety that they would rather hide than speak to someone else. Shyness is anxiety.

<https://www.nimh.nih.gov/health/publications/social-anxiety-disorder-more-than-just-shyness/index.shtml>

The reason this petition is for "Anxiety" and not "social anxiety disorder" is because each year there seems to be a new disorder with the core symptom being anxiety. Panic Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, PTSD. Anxiety is the common condition.

<https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml>

Any Anxiety Disorder with Impairment Among Adults

Of adults with any anxiety disorder in the past year, degree of impairment ranged from mild to severe, as shown in Figure 2. Impairment was determined by scores on the Sheehan Disability Scale.

Among adults with any anxiety disorder, an estimated 22.8% had serious impairment, and 33.7% had moderate impairment.¹

A majority of people with any anxiety disorder experienced mild impairment (43.5%).¹

1. Harvard Medical School, 2007. National Comorbidity Survey (NCS). (2017, August 21). Retrieved from <https://www.hcp.med.harvard.edu/ncs/index.php>. Data Table 2: 12-month prevalence DSM-IV/WMH-CIDI disorders by sex and cohort.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC181171/>

Although the principal symptoms of anxiety disorders include fear, excessive worry, nervousness, and obsessions, a multitude of physical symptoms also may be present. These somatic symptoms—which include heart palpitations, gastrointestinal problems, sweating, fainting, and chronic pain—can confound the diagnosis and resist all forms of medical management, unless the underlying anxiety source is identified and treated. Delays in diagnosis and treatment can be expensive for the patient, physician, and society: unnecessary tests and ineffective treatments increase medical costs, and **anxiety symptoms may lead to loss of income and productivity, financial dependence, and even suicide.**

(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.

N/A

(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.

(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.

Selected quotes and transcribed tables are taken from the following research and presented below.

1. <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.

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%).

3. <https://doi.org/10.1016/j.jpain.2007.09.002>

A randomized, double-blind, placebo-controlled trial was conducted to determine the benefit of nabilone in pain management and quality of life improvement in 40 patients with fibromyalgia.

There were significant decreases in the VAS, FIQ, and anxiety in the nabilone treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks, respectively. Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with

significant benefits in pain relief and functional improvement.

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

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.

5. <https://doi.org/10.1080/02791072.2011.587700>

Of 1,746 patients, 37.8% self-reported therapeutic benefits from medical marijuana for anxiety.

16.9% of patients self-reported therapeutic benefits from medical marijuana for panic attacks.

6. <https://www.ncbi.nlm.nih.gov/pubmed/6117575>

The results of the study showed a dramatic improvement in anxiety in the nabilone group when compared with placebo (P less than 0.001). Side effects reported were dry mouth, dry eyes, and drowsiness. Patients did not report any of the subjective "altered state" experience of marijuana.

7. <https://www.ncbi.nlm.nih.gov/pubmed/15857739>

Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), **anxiety (93%)**, nerve pain (90%), depression (86%), and paresthesia (85%).

8. <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.

9. <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.

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

Of 21 patients reporting stress, 20 said medical marijuana helped moderate-complete relief.
Of 16 patients reporting mood, all 16 said medical marijuana helped moderate-complete relief.
The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain.

11. <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.

12. <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.

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

367 medical marijuana patients in Arizona were surveyed.

181 patients reported using medical marijuana to experience relief from Anxiety

164 patients reported using medical marijuana to experience relief from Stress.

General relief from Anxiety symptoms was 82.9% and 87.2% for Stress,

Relief by medical marijuana compared to other medications was 79.3% for Anxiety and 91.6 for Stress.

Less frequent use of other medications was 85.9% for Anxiety and 79.1% for Stress.

14. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3285527/>

One Hundred Canadian medical marijuana patients were surveyed in 2007-2008. 60.2% said they used medical marijuana to reduce anxiety.

15. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1262744/>

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.

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.

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%).

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 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 . 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%).

16. <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.

17. <https://doi.org/10.1111/dar.12323>

Participants presented with the range of conditions that is generally consistent with surveys of CTP users, the most prominent conditions being pain (32%), mood (i.e. anxiety and depression (18%), arthritis (15%), HIV (10%), gastrointestinal disorder (7%)

18. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5422566/>

We previously reported in an earlier survey that of 1,429 respondents, 61% reported using cannabis for managing pain, 58% reported using cannabis for anxiety and 50% reported using cannabis for depression. In the current analysis, these same conditions were also the most commonly reported conditions by respondents. Of the 1,040 participants reporting pain and/or intractable pain, 619 (59.52%) reported depression and anxiety as comorbidities. As such, the odds of reporting substituting cannabis for prescription drugs were more than one and a half times greater (OR, 1.66; 95% CI,

1.27–2.16) among those reporting using it to manage pain, anxiety and depression than among those using it to manage only one of the three conditions.

This team previously reported that in a survey of 1,429 medical cannabis users, 61% reported cannabis use for pain, 58% reported cannabis use for anxiety and 50% reported using cannabis to manage depression. In 2016, Dale and Stacey reported that those using cannabis for pain were more likely to be substituting for prescription drugs. In 2017, Walsh et al published a review of medical cannabis and mental health to try to better understand how medical cannabis use may impact areas of potential concern for clinicians. "Relaxation and relief of anxiety" and "relief of negative mood" or depression were among the most widely reported conditions in 60 publications included in their analysis. Because it is common for chronic pain patients to be prescribed combinatorial pharmacotherapy to address comorbidity with depression and/or anxiety, it is largely unknown how often patients may be discontinuing prescription medications when initiating cannabis use.

Taken with preclinical data on the role of the endocannabinoid system in stress, pain processing and immune homeostasis, it is clear that future investigation is warranted using controlled trials with human subjects to better understand the role that cannabis may play in treating pain, anxiety, depression and other conditions.

19. <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.

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

Of 628 Canadian medical marijuana patients:

463 patients reported using medical marijuana to treat anxiety.

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.

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.

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.

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

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]

22. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3691841/>

While the controversies surrounding cannabis are far from subdued (and are often permeated and masked by conflicting ideological credos), standardized studies on cannabinoids have highlighted that the psychological and behavioral outcomes of this substance are highly variable and range from relaxation, euthymia and heightened sociability to panic, paranoid ideation and psychosis [112 - 116]. A corollary of this observation is that the high comorbidity rate between cannabis use disorders and psychiatric conditions [100 - 105] may indicate that cannabis consumption is either a concurring cause or a “self-therapeutic” strategy for anxiety and mood disorders [117 - 123]. The latter interpretation is supported by the observation that anxiety-spectrum disturbances and traumas in early developmental stages are a strong predictor for later cannabis use disorders [124 - 127]; furthermore, several lines of evidence suggest that the anxiolytic effects of THC may partially account for the high prevalence of cannabis use in patients affected by PTSD [128 - 131] and OCD [132]. Accordingly, recent clinical studies have shown that THC elicits therapeutic effects in OCD [133] and trichotillomania, an impulse-control disorder characterized by compulsive hair-pulling [134].

23. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604171/>

Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

24. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604174/>

Although clinical studies in this area are difficult to do, even in countries where the use of cannabis has been allowed for years, there is a clear role for cannabis products in symptom management for these difficult conditions.

25. <https://www.ncbi.nlm.nih.gov/pubmed/22729452>

RESULTS:

Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder.

CONCLUSION:

Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

26. <https://doi.org/10.2202/1941-2851.1017>

1655 Patients reported using medical marijuana for these conditions:
Anxiety disorders 18.7% of patients

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.

27. <https://doi.org/10.1176/appi.ajp.2007.07061016>

Hence, it can be speculated that the anti-obsessive effect observed in our patients may have been a consequence of the glutamate modulation of the cannabinoid dronabinol.

28. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4349825/>

The findings from the study indicate that cannabis use is associated with a subsequent change in positive affect, depressive symptoms and manic symptoms over the course of daily life. No evidence for the use of cannabis to self-

medicate minor fluctuations in negative affect or BD symptoms was revealed. Participants in the study were currently well and out of episode. Future research should explore whether the self-medication hypothesis is more relevant to individuals that are in the acute stages of depression or mania. This would be consistent with the broader self-medication hypothesis in BD where individuals have reported finding cannabis useful in the management of their symptoms.

29. <https://www.ncbi.nlm.nih.gov/pubmed/9692379>

The authors present case histories indicating that a number of patients find cannabis (marihuana) useful in the treatment of their bipolar disorder. Some used it to treat mania, depression, or both. They stated that it was more effective than conventional drugs, or helped relieve the side effects of those drugs. One woman found that cannabis curbed her manic rages; she and her husband have worked to make it legally available as a medicine.

Others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects. Another case illustrates the fact that medical cannabis users are in danger of arrest, especially when children are encouraged to inform on parents by some drug prevention programs. An analogy is drawn between the status of cannabis today and that of lithium in the early 1950s, when its effect on mania had been discovered but there were no controlled studies. In the case of cannabis, the law has made such studies almost impossible, and the only available evidence is anecdotal. The potential for cannabis as a treatment for bipolar disorder unfortunately can not be fully explored in the present social circumstances.

30. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4898690/>

Findings suggest that for some bipolar patients, marijuana may result in partial alleviation of clinical symptoms. Moreover, this improvement is not at the expense of additional cognitive impairment.

31. <https://www.ncbi.nlm.nih.gov/pubmed/17703715>

Subjective reports by patients suggest an overall positive effect, but these may be unreliable. We herein report a case in which mood data was prospectively collected over two years of total substance abstinence and two years of extreme marijuana use. Marijuana use did not alter the total number of days of abnormal mood, however, marijuana was associated with an increase in the number of hypomanic days and a decrease in the number of depressed days. While not conclusive, the data suggest that marijuana may indeed have an effect on mood in bipolar patients that needs to be systematically examined.

32. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652027/>

Cannabis use diminishes some of the adverse effects of neurological and psychiatric disorders.

33. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4323143/>

These results suggest that cannabis use has clinical implications for the early course of BD (Bipolar Disorder) by increasing mood level.

34. <https://doi.org/10.1111/j.1368-5031.2005.00271.x>

Medicinal cannabis use was Reported by patients with chronic pain(25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (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 in the United States. 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 anxiety.

In its first year of reports, the Minnesota DOH published patient comments about the beneficial effects of the medical marijuana.

(REF #98) <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>

Many such comments are found within the above report.

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

<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 anxiety symptoms, and a large percentage of patients continue to maintain that reduction of anxiety for 4 months.

(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 which show a very small percentage of people experience a worsening of anxiety symptoms. I urge you to read them all as it shows how small the number of adverse anxiety 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

Although the comments mention anxiety as a side effect, sometimes it is not the cannabis's fault, but prohibition's fault, as this comment rated at score level 4 shows:

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!

Massachusetts published a report on its medical marijuana patients and their benefits.

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

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

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

mood and or mental health for a large percentage of people.

Page 10:

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.

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.

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

N/A

Table of Contents

Appendix A: Patient-Reported Benefits from Surveys	A-2
Severe and Persistent Muscle Spasms	A-2
Cancer.....	A-17
Seizures	A-22
Crohn’s Disease	A-28
Terminal Illness	A-30
HIV/AIDS.....	A-32
Tourette Syndrome	A-33
Glaucoma	A-33
ALS	A-34

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.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- 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 juristically 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 giving 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



Revista Brasileira de Psiquiatria

RBP Psychiatry

Official Journal of the Brazilian Psychiatric Association
Volume 34 • Supplement 1 • June/2012



ARTICLE

Cannabidiol, a *Cannabis sativa* constituent, as an anxiolytic drug

Alexandre Rafael de Mello Schier,¹ Natalia Pinho de Oliveira Ribeiro,¹
Adriana Cardoso de Oliveira e Silva,^{1,2,4} Jaime Eduardo Cecilio Hallak,^{3,4}
José Alexandre S. Crippa,^{3,4} Antonio E. Nardi,^{1,4} Antonio Waldo Zuardi^{3,4}

¹ Laboratory of Panic and Respiration, Institute of Psychiatry (IPUB), Universidade Federal do Rio de Janeiro (UFRJ), Brazil

² Universidade Federal Fluminense, Brazil

³ Department of Neuroscience and Behavioral Sciences, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Brazil

⁴ Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (National Institute for Translational Medicine; INCT-TM), Brazil

Received on March 2, 2011; accepted on December 18, 2011

DESCRIPTORS

Cannabidiol;
Cannabis sativa;
Anxiolytics;
Anxiety disorders.

Abstract

Objectives: To review and describe studies of the non-psychotomimetic constituent of *Cannabis sativa*, cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action. **Method:** The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO, combining the search terms “cannabidiol and anxiolytic”, “cannabidiol and anxiolytic-like”, and “cannabidiol and anxiety”. The reference lists of the publications included, review articles, and book chapters were handsearched for additional references. Experimental animal and human studies were included, with no time restraints. **Results:** Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder. **Conclusion:** Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

Introduction

Cannabis sativa is the most used drug of abuse worldwide and around 20% of youth use it heavily and regularly around the globe.¹ The main psychoactive component of the plant is Δ 9-tetrahydrocannabinol (Δ 9-THC), one of the substances responsible for the psychoactive effects of Cannabis.²⁻⁴

Cannabidiol (CBD) is another abundant compound in *Cannabis sativa*, constituting around 40% of the plant's active substances.⁵ The pharmacological effects of CBD are different and often opposite to those of Δ 9-THC.⁶ The number of publications on CBD has increased remarkably over the last years and support the view that CBD has a vast array of possible therapeutic effects. Among these possibilities, the anxiolytic and antipsychotic properties of CBD stand out.⁷⁻¹⁰ CBD's anxiolytic effects are apparently similar to those of approved drugs to treat anxiety,¹¹ although its effective doses have not been clearly established and the mechanisms underlying these effects are not fully understood. The low affinity of CBD for cannabinoid neuroreceptors^{12,13} and its agonist properties at 5-HT_{1A} receptors^{14,15} have been repeatedly demonstrated.

Most studies on CBD have been conducted with rodents, but studies with human samples have also provided promising results.^{16,17} Therefore, the aim of this paper is to review the scientific literature on the anxiolytic properties of CBD in animal and in humans.

Method

The articles selected for this review were identified by searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". In addition, the reference lists of the selected articles and relevant literature reviews and book chapters were handsearched for additional references. We included experimental studies with human and animal samples with no time limits. We sought to exclude studies that used smoked Cannabis, as it is not possible to establish the dose, composition, and proportion of the different cannabinoids in this case, besides the great individual variations in the samples enrolled. Finally, we did not include studies using extracts containing both THC and CBD in oral (Cannador®) or oromucosal spray (Sativex®) forms due to the difficulty to establish the effects of CBD alone (Table 1).

Animal studies

The two first articles about the effects of CBD on experimental anxiety were published in journals that were not indexed in the databases used for this review but were located through handsearch in the reference lists of relevant literature. These two investigations showed contradictory results. In one study, no significant effects of high doses of CBD (100 mg/kg) were seen in rats in the Geller-Seifter conflict test.¹⁸ In the other, a low dose of CBD (10 mg/kg) had anxiolytic effects in rats submitted to the conditioned emotional response test.¹⁹

Later studies using the elevated plus maze (EPM) helped to elucidate this contradiction.⁹ The EPM consists of two opposing open arms (50 x 10 cm) and two closed arms

(50 x 10 x 40 cm) that intersect in their central portion. The arms are made of wood and stand 50 cm above the ground. In this study, mice injected with CBD, diazepam or vehicle (no active substances) were placed in the center of the maze facing the closed arms. The time spent and the numbers of entries in the open and closed arms were measured for 10 minutes. The frequency of entries in the open arms of animals receiving CBD presented an inverted U-shaped curve, with significantly higher rates than those observed in animals treated with vehicle, at the doses of 2.5, 5, and 10 mg/kg. The measures of mice treated with CBD 20 mg/kg did not differ from those of controls, suggesting that anxiolytic effects are only present at low doses, which explains the absence of effects with CBD 100 mg/kg reported in 1981.¹⁸ The same inverted U-shaped dose-response curve was obtained with a wider range of doses of CBD in the EPM (Onaivi et al.).²⁰ Furthermore, the same pattern was observed with the direct infusion of CBD in the periaqueductal gray (PAG) of rats tested in the EPM,^{15,21} confirming that anxiolytic effects should only be expected with low doses of CBD.

The mechanisms through which CBD acts to diminish anxiety have been studied in a number of animal models of anxiety using rodents. One of these studies used Vogel's conflict test,²² in which the animal is water-deprived from and placed in a cage with an electrified grid at the bottom through which the animal receives a shock after licking water for a predetermined number of times. Three substances were tested in rats using the following procedure: CBD (2.5, 5 and 10 mg/kg), diazepam, and flumazenil (an antagonist of benzodiazepine receptors), in addition to vehicle (placebo). The tests showed that CBD produced effects consistent with those of diazepam by increasing the number of licks, even if they resulted in punishment. Flumazenil antagonized the anxiolytic effect of diazepam, but not that of CBD, suggesting that the effects of CBD are not mediated by the activation of benzodiazepine receptors.

There is strong evidence showing that the serotonergic system is involved in the anxiolytic action of CBD. The injection of the 5-HT_{1A} receptor antagonist WAY-100635 (WAY) directly into the dorsolateral portion of the PAG (dIPAG) in rats antagonized the anxiolytic effects of CBD in the EPM and in Vogel's conflict test.¹⁵ The participation of 5-HT_{1A} receptors in the anxiolytic action of CBD was also derived from behavioral and cardiovascular responses to restraint stress in rats.¹¹ In this study, animals were intraperitoneally injected with vehicle or CBD (1, 10 and 20 mg/kg) and, after 30 minutes, they were restrained for 60 minutes. Immobilization increased blood pressure, heart rate, and anxiety responses in the EPM 24 hours later, and these effects were attenuated by CBD. Pretreatment with WAY blocked the anxiolytic action of CBD. The injection of CBD into the intra-dorsal PAG also blocked panic-like responses in the elevated T-maze (ETM) and flight responses to the electrical stimulation of this area.²³ The ETM has three arms with the same dimensions, two open and one closed, and allows the measure of entrance avoidance in the open arms when the animal is placed in the closed arm, as well as of escape when the animal is placed in the open arm. The panic-like response seen with CBD in the two procedures was antagonized by the previous intra-dIPAG administration of WAY.²² Chronic oral administration of CBD also had anti-panic effects in the ETM that were neutralized

Table 1 Studies of the anxiolytic effect of cannabidiol in humans and animals

Study	Model	Route	Dose	Anxiolytic effect
Animals				
Silveira Filho et al. ¹⁸	Conflict test	Intraperitoneal	100 mg/kg	-
Zuardi et al. ¹⁹	Conditioned emotional response paradigm	Intraperitoneal	10 mg/kg	+
Onaivi et al. ²⁰	Elevated plus maze test	Intraperitoneal	0.01, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 50.0 and 100.0 mg/kg	+
Guimarães et al. ⁹	Elevated plus maze test	Intraperitoneal	2.5, 5.0, 10.0 and 20.0 mg/kg	+
Moreira et al. ²²	Vogel's conflict test	Intraperitoneal	2.5, 5.0 and 10.0 mg/kg	+
Resstel et al. ¹⁰	Contextual fear conditioning	Intraperitoneal	10 mg/kg	+
Campos et al. ¹⁵	Elevated plus maze test and Vogel's conflict test	Intra-dorsal periaqueductal gray		+
Bitencourt et al. ²⁸	Contextual fear conditioning	i.c.v.	2.0 microg/microl	+
Campos et al. ²¹	Elevated plus maze test	Intra-dorsal periaqueductal gray	30 or 60 nmol	+
Resstel et al. ¹⁹	Restraint stress	Intraperitoneal	1, 10 and 20 mg/kg	+
Soares et al. ²³	Elevated T maze	Intra-dorsal periaqueductal gray	15, 30 or 60 nmol	+
Lemos et al. ²⁹	Contextual fear conditioning	Intraperitoneal and direct microinjection into the PL prefrontal cortex	10 mg/kg (i.p.) and 30 nmol (microinjection into the PL prefrontal cortex)	+
Casarotto et al. ²⁶	Marble-burying test	Intraperitoneal	15, 30 and 60 mg/kg	+
Gomes et al. ³⁰	Vogel's conflict test	Intra bed nucleus of the stria terminalis	15, 30, and 60 nmol	+
Deiana et al. ²⁷	Marble-burying test	Intraperitoneal and oral	120 mg/kg	+
Uribe-Mariño et al. ³¹	Prey-predator paradigm	Intraperitoneal	0.3, 3.0 and 30 mg/kg	+
Campos et al. ²⁴	Elevated T maze	Oral		+
Humans				
Zuardi et al. ⁷	Decreased STAI scores elevation induced by THC (healthy volunteers)	Oral	1 mg/kg	+
Zuardi et al. ³²	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	Oral	300 mg	+
Crippa et al. ³⁴	Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)	Oral	400 mg	+
Fusar-Poli et al. ³⁵	Decreased skin conductance fluctuation in task with fearful faces during a fMRI procedure (healthy volunteers)	Oral	600 mg	+
Crippa et al. ¹⁷	Decreased VAS factor anxiety scores before SPECT procedure (social phobia patients)	Oral	400 mg	+
Bergamaschi et al. ³³	Decreased VAS factor anxiety scores after public speaking (social phobia patients)	Oral	600 mg	+

by intra-dlPAG injection of WAY. However, chronic administration of CBD did not change the extracellular concentration of serotonin in the dlPAG or the expression of 5-HT1A or 5-HT2C, indicating that CBD directly activates 5-HT1A receptors.²⁴ CBD was also found to activate the vanilloid receptor type 1 (TRPV1)²⁵ and there is evidence that this activation could explain the inverted U-shaped dose-response curve of CBD's anxiolytic effect seen in the EPM. TRPV1 receptors regulate the release of glutamate in the dlPAG and the increased activation of this system would result in increased anxiety. Thus, it has been suggested that elevated doses of CBD in the dlPAG could activate local TRPV1 receptors facilitating the glutamatergic neurotransmission and increasing anxiety.

To test this hypothesis, rats pre-treated with the TRPV1 antagonist capsazepine in the dlPAG were injected with CBD (30 and 60 mg/kg) in the same region and tested in the EPM. The dose of 60 mg/kg CBD, which had no anxiolytic action before, was able to reduce anxiety after pre-treatment with capsazepine, suggesting that the activation of TRPV1 receptors by the higher dose of CBD would counterbalance the anxiolytic effect of CBD produced by the activation of 5-HT1A receptors.²¹

Because serotonin has also been implicated in obsessive-compulsive disorder (OCD), the effects of CBD were tested in mice submitted to the marble-burying test (MBT), an animal model of compulsive behavior. CBD induced a significant reduction in the number of buried marbles at different doses (15, 30, and 60 mg/kg) compared to controls in a dose-dependent pattern. The same was found with the administration of the ISRS paroxetine (10 mg/kg) and diazepam (2.5 mg/kg). However, the effects of CBD 30 mg/kg persisted even after seven days of repeated daily administration, whereas the effects of diazepam disappeared. Pre-treatment with WAY (3 mg/kg) counteracted the effects of paroxetine, but did not affect the action of CBD, which was prevented by pre-treatment with the CB1 receptor antagonist AM251 (1 mg/kg).²⁶ This action of CBD in the MBT was recently replicated by another group using a higher dose (120 mg/kg).²⁷

The participation of specific cannabinoid receptors (CB1) in the anxiolytic action of CBD has also been investigated using animal models. In the study with the EPM that reported the antagonism of the anxiolytic effect of intra-dlPAG CBD by WAY, the CB1 receptor antagonist AM251 was unable to avoid this effect.¹⁵ However, this receptor system seems to be involved in another anxiolytic-like action of CBD, according to tests using a procedure known as contextual fear conditioning. In this procedure, animals are pre-conditioned to a hostile environment (foot shocks) and later exposed to the same environment, when they normally present freezing, the duration of which can be monitored as a measure of anxiety. Both CBD and diazepam are successful in attenuating freezing in rats, as well as the increased heart rate and blood pressure induced by re-exposure to the contextually feared environment.¹⁰ This effect of CBD on contextual memory is also produced by the endocannabinoid reuptake inhibitor AM404, which increases the availability of cannabinoids in the synaptic cleft.²⁸ In this study, the two drugs were injected into the ventricles and their effects were counteracted by the CB1 receptor antagonist SR141716A, suggesting the involvement of the endocannabinoid system in the anxiolytic action of CBD in this model. The pre-limbic region of the prefrontal cortex

appears to underlie this effect of CBD, as the reduction in contextual fear produced by systemic administration of CBD (10 mg/kg) is associated with reduced c-Fos expression in this area. In addition, the microinjection of CBD (30 nmol) in the pre-limbic region of the frontal cortex reduced freezing induced by re-exposure to the aversive context.²⁹ The effects of CBD on contextual fear indicate a possible therapeutic action of this cannabinoid in post-traumatic stress disorder.

Another area that is apparently involved in the anxiolytic-like effects of CBD is the bed nucleus of the stria terminalis (BNST). The intra-BNST injection of CBD (15, 30, and 60 nmol) increased the number of punished licks in Vogel's conflict test and the number of open arm entries in the EPM. These effects were blocked in rats pre-treated with WAY.³⁰

CBD was also effective in an ethologic model that investigates behaviors induced by innate fear, the predator-prey paradigm.³¹ This procedure was performed using a semi-transparent plexiglass box in the shape of a quadrangular arena (154x72x64 cm) with walls covered with a light-reflecting film and floor in transparent plexiglass over a board of stainless steel divided in 20 equal rectangles. One of the corners of the arena has a shelter box with black walls and a complex maze inside. Three days prior to the experiment, the mice were placed and kept in this arena, with free access to food and water until the day of the trial. The "no threat" group had its behaviors recorded for five minutes. Animals exposed to the predator (snake) were divided into four groups (n = 12/11 per group) and pre-treated with intraperitoneal injections of CBD (0.3, 3 and 30 mg/kg) or vehicle (control group). The group of animals that were not confronted with the predator presented no defensive behaviors. Animals pre-treated with CBD had significant reductions in explosive flight and defensive immobility, responses related to panic models. Risk assessment and defensive attention were unaltered in animals treated with CBD. These results suggest that CBD can be effective in the control of panic attacks.

Human studies

The first evidence of CBD's anxiolytic effects in humans, documented with assessment scales, was published in 1982 in a study on the interaction between CBD and THC.⁷ The study sample consisted of eight volunteers with a mean age of 27 years, no health problems and who had not used *Cannabis sativa* in the previous 15 days. In a double-blind procedure, the volunteers received CBD, THC, THC + CBD, diazepam, and placebo in different sequences and days. The results showed that the increased anxiety following the administration of THC was significantly attenuated with the simultaneous administration of CBD (THC + CBD).

Based on this preliminary evidence, researchers decided to investigate a possible anxiolytic action of CBD in experimentally induced anxiety in healthy volunteers using the simulated public speaking (SPS) model.³² The procedure consists of asking a subject to speak in front of a video camera for a few minutes, while subjective anxiety is measured with self-rated scales and physiological correlates of anxiety are recorded (heart rate, blood pressure, skin conductance). CBD (300 mg), as well as the anxiolytic drugs diazepam (10 mg) and ipsapirone (5 mg), administered in a double-blind design, significantly attenuated SPS-induced anxiety.

The SPS test may be regarded as a good model of anxiety and has apparent validity for social anxiety disorder (SAD), as the fear of speaking in public is considered a central feature in this condition. Therefore, the anxiolytic effect of CBD in healthy volunteers observed in this test led to the hypothesis that this cannabinoid could be effective to treat SAD. This hypothesis was recently tested in 24 patients with SAD who had their performance in the SPS test compared to that of a group of 12 healthy controls.³³ The patients with SAD were divided into two groups of 12, one of which received CBD 600 mg and the other placebo, in a double-blind procedure. The results showed that the levels of anxiety, somatic symptoms, and negative self-assessment were higher in patients who took placebo than in those of the CBD group who performed similarly to healthy controls in some measures.

In another study that investigated the effects of CBD on regional cerebral blood flow (rCBF) in healthy volunteers using single photon emission computed tomography (SPECT), SPS-induced anxiety was reduced in patients receiving CBD.³⁴ In that study, patients received either CBD (400 mg) or placebo, in a crossed double-blind design, in two experimental sessions with an interval of one week. CBD significantly reduced subjective anxiety as measured by rating scales, while brain activity was increased in the left parahippocampal gyrus and decreased in the left amygdala-hippocampus complex, including the fusiform gyrus. This pattern of SPECT results is compatible with an anxiolytic action.

SPECT was also used later to investigate the neural correlates of CBD's anxiolytic effects in a sample of patients with SAD.¹⁷ A single dose of CBD 400 mg was able to reduce subjective anxiety measures and SPECT showed changes in the same regions previously identified in healthy volunteers.

Functional magnetic resonance imaging (fMRI), which allows the acquisition of larger series of images with better temporal and spatial resolution, was used to investigate the neural correlates of the anxiolytic effects of CBD in 15 healthy volunteers.³⁵ This experiment showed that CBD (600 mg) attenuated fMRI responses during the recognition of fearful facial expressions in the amygdala and the anterior cingulate, and that this attenuation pattern correlated with skin conductance responses to the stimuli. The same group also reported that the anxiolytic action of CBD occurs by altering the subcortical prefrontal connectivity via amygdala and anterior cingulate.¹⁶

Conclusion

Together, the results from laboratory animals, healthy volunteers, and patients with anxiety disorders support the proposition of CBD as a new drug with anxiolytic properties. Because it has no psychoactive effects and does not affect cognition; has an adequate safety profile, good tolerability, positive results in trials with humans, and a broad spectrum of pharmacological actions,³⁶ CBD appears to be the cannabinoid compound that is closer to have its preliminary findings in anxiety translated into clinical practice.³⁷ Future studies should test this possibility in clinical trials involving patients with different anxiety disorders, especially panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorder. In addition, because the actions of CBD are biphasic, the adequate therapeutic window for each anxiety disorder remains to be determined.

Regarding the mechanism underlying the anxiolytic effects of CBD, the most consistent evidence points to the involvement of the serotonergic system, probably through direct action on 5-HT_{1A} receptors, although other systems, as the endocannabinoid system itself, may also be implicated. Further investigation is warranted to clarify these issues, especially if we consider that CBD is a drug with a variety of effects in the nervous system.³⁸⁻⁴⁰

Disclosures

Alexandre Rafael de Mello Schier

Employment: Universidade Federal do Rio de Janeiro (UFRJ), Brazil. **Research grant:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq)*, Brazil. **Other:** Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ), Brazil.

Natalia Pinho de Oliveira Ribeiro

Employment: Universidade Federal do Rio de Janeiro (UFRJ), Brazil. **Research grant:** Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes)*, Brazil. **Other:** Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ), Brazil.

Adriana Cardoso de Oliveira e Silva

Employment: Universidade Federal Fluminense (UFF), Brazil. **Other:** Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ); National Institute for Translational Medicine (INCT-TM), Brazil.

Jaime Eduardo Cecílio Hallak

Employment: Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil. **Research grant:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil. **Other:** THC-Pharm, Novartis, AstraZeneca; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.

José Alexandre S. Crippa

Employment: Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil. **Research grant:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil. **Other:** THC-Pharm, Elli-Lilly, Servier; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.

Antonio E. Nardi

Employment: Universidade Federal do Rio de Janeiro (UFRJ), Brazil. **Research grant:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq)**, Brazil. **Speaker's honoraria:** Glaxo-Smiskline*, Roche. **Consultant/ Advisory board:** Aché*. **Other:** ArtMed*; Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ); National Institute for Translational Medicine (INCT-TM), Brazil.

Antonio Waldo Zuardi

Employment: Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil. **Research grant:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil. **Other:** THC-Pharm; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.

* Modest

** Significant

*** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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Nabilone for the Treatment of Pain in Fibromyalgia

Ryan Quinlan Skrabek, Lena Galimova, Karen Ethans, and Daryl Perry

Section of Physical Medicine and Rehabilitation, University of Manitoba, Rehabilitation Hospital, Health Sciences Centre, Winnipeg, Manitoba, Canada.

Abstract: A randomized, double-blind, placebo-controlled trial was conducted to determine the benefit of nabilone in pain management and quality of life improvement in 40 patients with fibromyalgia. After a baseline assessment, subjects were titrated up on nabilone, from 0.5 mg PO at bedtime to 1 mg BID over 4 weeks or received a corresponding placebo. At the 2- and 4-week visits, the primary outcome measure, visual analog scale (VAS) for pain, and the secondary outcome measures, number of tender points, the average tender point pain threshold, and the Fibromyalgia Impact Questionnaire (FIQ), were evaluated. After a 4-week washout period, subjects returned for reassessment of the outcome measures. There were no significant differences in population demographics between groups at baseline. There were significant decreases in the VAS (-2.04 , $P < .02$), FIQ (-12.07 , $P < .02$), and anxiety (-1.67 , $P < .02$) in the nabilone treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks (1.58 , $P < .02$ and 1.54 , $P < .05$), respectively. Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with significant benefits in pain relief and functional improvement.

Perspective: To our knowledge, this is the first randomized, controlled trial to assess the benefit of nabilone, a synthetic cannabinoid, on pain reduction and quality of life improvement in patients with fibromyalgia. As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia.

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Key words: Nabilone, cannabinoid, fibromyalgia, pain.

Fibromyalgia is a syndrome of unknown etiology, characterized by diffuse musculoskeletal pain, fatigue, and sleep disturbance.³⁸ It affects 2% to 4% of the general population^{35,36,37} and is 4 to 7 times more common in women, with symptoms usually arising between 20 and 55 years of age.¹⁵

The diagnostic criteria for fibromyalgia, established in 1990 by the American College of Rheumatology, includes widespread pain for at least 3 months and point tenderness with 4 kg of pressure at 11 or more of 18 characteristic tender points.³⁸ These criteria allow for the

differentiation of fibromyalgia from other chronic musculoskeletal pain with a sensitivity and specificity of almost 85%.¹⁶

Patients with fibromyalgia have lower pain thresholds to both mechanical and thermal insults, give higher pain ratings, and experience an altered temporal summation to painful stimuli.¹⁶ The sensitization of pain perception that is present in these patients can occur both peripherally and centrally after tissue damage but may also be present in patients with no obvious tissue damage.²⁰ Sensitization occurs in the dorsal horn of patients with fibromyalgia, as activity of both unmyelinated C fibers and A- δ fibers is increased^{14,21}; however, it is unknown whether sensitization is due to increased pain fiber facilitation, or decreased inhibition.²⁰

Given the lack of understanding in the pathophysiology of fibromyalgia, it is not surprising that until recently, with the approval of pregabalin, no medical treatment had been specifically approved by the United States Food and Drug Administration for its management.¹³ There is also evidence that tricyclic antidepressants, cardiovascular exercise, cognitive behavioral therapy and patient

Received April 19, 2007; Revised August 27, 2007; Accepted September 26, 2007.

Supported by an unrestricted research grant provided by Valeant Canada Limited and an HSC Medical Staff Council Fellowship Fund. Valeant Canada Limited had no involvement in study design, interaction with patients, patient assessments, data analysis, or the authorship of this paper. Address reprint requests to Dr. Ryan Quinlan Skrabek, Physical Medicine and Rehabilitation, PGY4, Rehabilitation Hospital, RR133-800 Sherbrook Street, Winnipeg, Manitoba, Canada, R3A 1M4. E-mail: rskrabek@hotmail.com

1526-5900/\$34.00

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doi:10.1016/j.jpain.2007.09.002

education are effective in reducing the pain experienced by fibromyalgia patients.¹⁶ A recent case series of 4 patients has suggested the possible benefit of nabilone, a synthetic cannabinoid, in the treatment of fibromyalgia, however more studies are required.¹⁸

Two types of cannabinoid receptors have been isolated: CB1 and CB2. The CB1 receptor is found predominantly in the central and peripheral nervous system,²⁵ whereas CB2 receptors are found principally in the immune system.²⁷ Endogenous cannabinoids have been isolated that interact with these receptors.¹⁰ CB1 agonists have been shown to have an analgesic effect in acute and chronic pain models.¹⁰ The CB1 agonists act at many sites along pain transmission pathways including activation of peripheral, spinal, and supraspinal CB1 receptors, each independently decreasing nociception.¹⁰

The endocannabinoid system shares several similarities with the opioid system.⁹ CB1 and opioid receptors are both found in similar areas of the nervous system involved in pain control, including the periaqueductal gray matter, rostral ventromedial medulla, and the spinal cord.²⁹ Besides the similarities with the opioid system, cannabinoids have also been shown to inhibit prostaglandin E-2 synthesis,⁸ reduce platelet aggregation,³¹ and have an anti-inflammatory effect twice as great as hydrocortisone and 20 times that of aspirin.¹²

Nabilone is 1 of 2 orally administered cannabinoids available in Canada and is currently approved for the management of nausea and vomiting during chemotherapy. Research into oral cannabinoid use in the management of chronic and neuropathic pain has been encouraging.^{18,32} As no treatment has been specifically approved for management of fibromyalgia, further research into treatment strategies is important. To date, no randomized, controlled trials have been conducted to assess the efficacy of a synthetic cannabinoid on pain and quality of life in patients with fibromyalgia.

Our hypothesis was that nabilone will significantly reduce the pain and improve quality of life in fibromyalgia patients compared with placebo, as evidenced by significant improvements in visual analog scale pain scores (VAS), number of tender points, average tender point pain threshold, and scores on the Fibromyalgia Impact Questionnaire (FIQ).

Materials and Methods

Setting

The study was conducted in the Outpatient Musculoskeletal Clinic at the Rehabilitation Hospital, Health Sciences Centre (HSC), Department of Physical Medicine and Rehabilitation, in Winnipeg, Manitoba, Canada, from April 2006 to November 2006. Patients were recruited from the musculoskeletal practices of attending Physiatrists and Rheumatologists at the Rehabilitation Hospital.

Inclusion Criteria

Inclusion criteria for the study included the subject meeting The American College of Rheumatology (1990)

criteria for the classification of fibromyalgia³⁸; patients between 18 and 70 years of age; having continued pain despite the use of other oral medications; and no previous use of oral cannabinoids for pain management.

Exclusion Criteria

Subjects were excluded from participating in the study if their pain was better explained by a diagnosis other than fibromyalgia; for abnormalities on routine baseline blood work including electrolytes, urea and creatinine, a complete blood count, and liver function tests; heart disease; schizophrenia or other psychotic disorder; severe liver dysfunction; history of untreated nonpsychotic emotional disorders; cognitive impairment; major illness in another organ system; pregnancy; nursing mothers; a history of drug dependency; or a known sensitivity to marijuana or other cannabinoid agents.

Protocol

Subjects met the eligibility criteria through a structured interview process, and participants provided informed consent. HSC Research ethics board, HSC Impact Committee and Health Canada approval was obtained prior to proceeding with the study.

Subjects were randomly assigned by the HSC pharmacy into treatment and control groups, each consisting of 20 participants (Fig 1). The examining physicians and the subjects were blinded to the randomization process. All of the study medication was provided by Valeant Canada Limited (Montreal, Quebec, Canada) and was identical to placebo. Subjects in both groups were seen at baseline, after 2 weeks and 4 weeks of treatment and after a 4-week washout period. Subjects in the treatment group received 0.5 mg nabilone PO at bedtime for a 1-week period, with instructions to increase to 0.5 mg BID after 7 days. At the 2-week visit, subjects were evaluated for the presence of side effects and drug tolerance, and if they consented to continue, had the prescription increased to nabilone 0.5 mg PO in the morning and 1 mg PO at bedtime, with instructions to increase to 1 mg BID after 7 days. Subjects in the control group received a corresponding placebo. Subjects were assessed for the safety and efficacy of their prescription based on the outcome measures at the 2-, 4-, and 8-week follow-up visits. Subjects were asked to continue any current treatment for fibromyalgia, including breakthrough pain medications, but not to begin any new therapies.

Outcome Measures

The primary outcome measure was a 10 cm VAS for pain. The secondary outcome measures included the number of positive tender points; the average tender point pain threshold; and the subject's score on the FIQ.

At each visit, subjects were asked to rate their current level of pain on the 10 cm VAS, (0 = no pain; 10 = worst pain imaginable), a valid and reliable scale for rating pain intensity.²⁶ Subjects then filled out the FIQ, which is a validated, self-administered test, scored out of 100, that evaluates physical function, work status, depression,

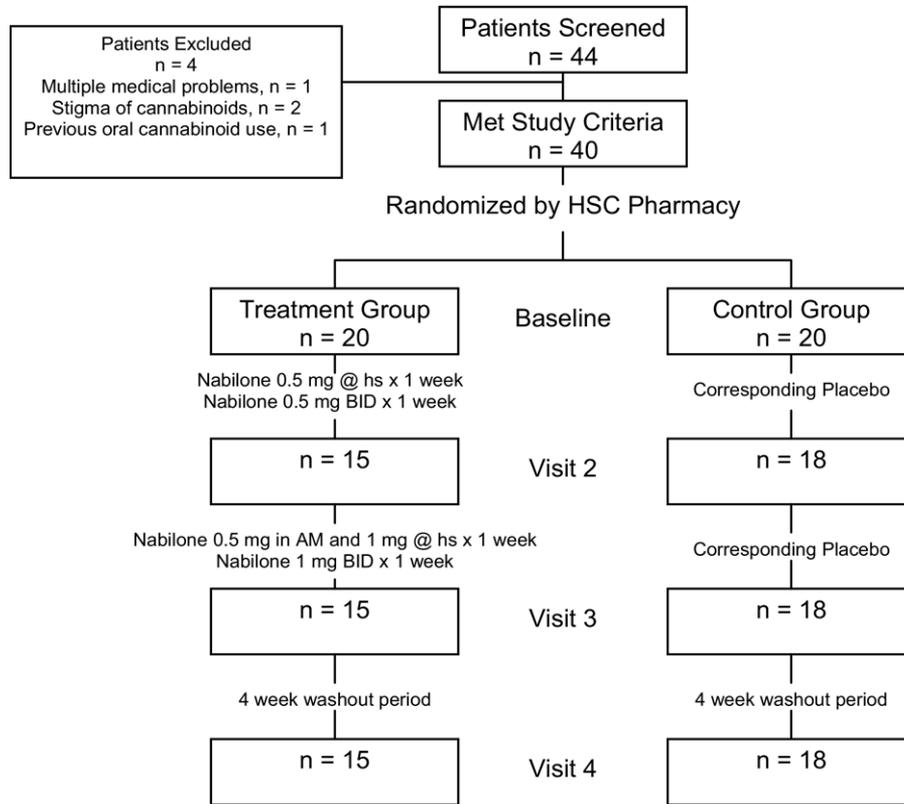


Figure 1. Study design. A randomized, double-blind, placebo-controlled trial.

anxiety, sleep, pain, stiffness, fatigue, and well-being in patients with fibromyalgia.^{7,23} The higher the score on the FIQ, the greater the impact of fibromyalgia on the subject's quality of life.⁷ Subjects were then assessed for the number of positive tender points by digital palpation over the 18 characteristic tender point sites in the ACR criteria for the diagnosis of fibromyalgia,³⁸ which has been previously shown to have both good intrarater and interrater reliability.³³ The subjects were asked to identify if a given point was painful as slow steady digital pressure was applied. The same evaluation of the tender points was then repeated with a hand-held Fischer algometer. This test has also demonstrated good interrater and test-retest reliability.³³ Pressure was applied over each tender point at a rate of 1 kilogram per square centimeter per second, and subjects were asked to identify the moment the pressure became painful. The pain threshold at each of the 18 tender points was recorded and an average tender point pain threshold for each visit was calculated. During each visit, any reported side effects as well as weight, blood pressure, and heart rate were recorded.

Statistical Analysis

Based on the previous case series investigating nabilone use in fibromyalgia,¹⁸ we calculated that 16 patients would be necessary in each group to detect a change of 2 cm on the 10 cm VAS, using an α of <0.05 and a power of 80%. Allowing for dropouts, our aim was

to have 20 subjects in each group start the study. Statistical analysis was conducted, and we considered $P < .05$ to be statistically significant for all of our outcome measures. The mean and standard deviation was calculated for each outcome measure at each visit and a Student's *t* test was performed to compare the change in the mean from baseline within and between groups.

Results

Forty-four subjects were screened to participate in the study between April and November of 2006. Four subjects did not meet the entrance requirements for the study. Reasons for their exclusion included a history of multiple medical problems ($n = 1$); subjects did not like the stigma associated with the use of cannabinoids ($n = 2$); and previous oral cannabinoid use ($n = 1$).

The remaining 40 subjects were randomly assigned by the HSC pharmacy into either the nabilone or placebo group (Fig 1). The examining physicians and patients were blinded to the randomization process. The baseline demographic data and baseline outcome measures are presented for both groups (Table 1). No significant differences in baseline demographic data or primary and secondary outcome measures were present. The percentage of subjects employed and the use of opioid medications for pain were not significantly different between the 2 groups.

A total of 5 subjects from the treatment group and 2

Table 1. Baseline Demographics and Outcome Measures for the Nabilone and Placebo Groups (Mean \pm SD)

PATIENT DEMOGRAPHICS AND BASELINE OUTCOME MEASURES	TREATMENT GROUP N = 20 (20 F:0 M)	PLACEBO GROUP N = 20 (17 F:3 M)	MEAN DIFFERENCE	P VALUE SIGNIFICANT < .05
Age (years)	47.6 \pm 9.13	50.11 \pm 5.96	2.51	> .15
Height (inches)	64.30 \pm 1.86	64.74 \pm 4.24	0.44	> .25
Weight (kg)	89.42 \pm 24.54	79.85 \pm 14.36	9.57	> .10
VAS (cm)	6.86 \pm 2.14	6.2 \pm 1.46	0.66	> .15
Number of tender points	15.73 \pm 3.01	15.67 \pm 2.03	0.06	> .25
Pain threshold (kg/cm ²)	1.41 \pm 0.51	1.51 \pm 0.60	0.1	> .25
FIQ score	66.45 \pm 12.76	66.53 \pm 16.21	0.08	> .25
Anxiety score	5.87 \pm 1.72	5.39 \pm 2.14	0.48	> .20
Depression score	5.47 \pm 2.33	5.28 \pm 2.42	0.19	> .25
Fatigue score	8.20 \pm 1.51	7.50 \pm 2.65	0.70	> .20

Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; VAS, visual analog score.

from the placebo group dropped out of the study before its completion. All of the subjects who withdrew from the study did so at or before the first follow-up visit. In the control group, one subject discontinued the medication after 4 days because of headaches; the other withdrew at the first follow-up visit, after 2 weeks, although no side effects or reason for dropping out was stated. Of the subjects in the treatment group, 3 withdrew before the first follow-up visit. Two of these subjects did not state a reason for withdrawal and listed no side effects, whereas the other subject experienced dizziness, disorientation, and nausea. The remaining 2 subjects in the treatment group to withdraw did so at the first follow-up visit, after 2 weeks. One subject stated poor coordination, dizziness, headache, and nausea as the reasons for withdrawing from the study, whereas the other experienced drowsiness and fatigue. All patients in the treatment group that continued with the study achieved a nabilone dose of 1 mg BID.

There was a significant increase in the weight of subjects treated with nabilone for 2 weeks, (1.13 kg, $P < .01$).

This effect, however, was transient, as there was no significant difference in weight change observed between the 2 groups during the 4-week and 8-week visits.

When compared with baseline, at the 2-, 4-, and 8-week visits, no statistically significant differences were observed in any of the outcome measures in the placebo group.

There were no statistically significant differences from baseline in the outcome measures in the nabilone treated subjects, at a dose of 0.5 mg BID, after 2 weeks of treatment. However, at the 4-week follow-up visit, at a nabilone dose of 1 mg BID, statistically significant improvements were seen in the VAS, FIQ, and FIQ anxiety scale. The VAS scores for pain decreased from baseline at 4 weeks (-2.04 , $P < .02$) (Fig 2). Fibromyalgia Impact Questionnaire scores also significantly decreased (-12.07 , $P < .02$) (Fig 3). The 10-point anxiety scale within the FIQ was the final outcome to be statistically improved from baseline after 4 weeks of treatment (-1.67 , $P < .02$) (Fig 4). The remaining outcomes we assessed including number of tender points, tender point pain threshold, and

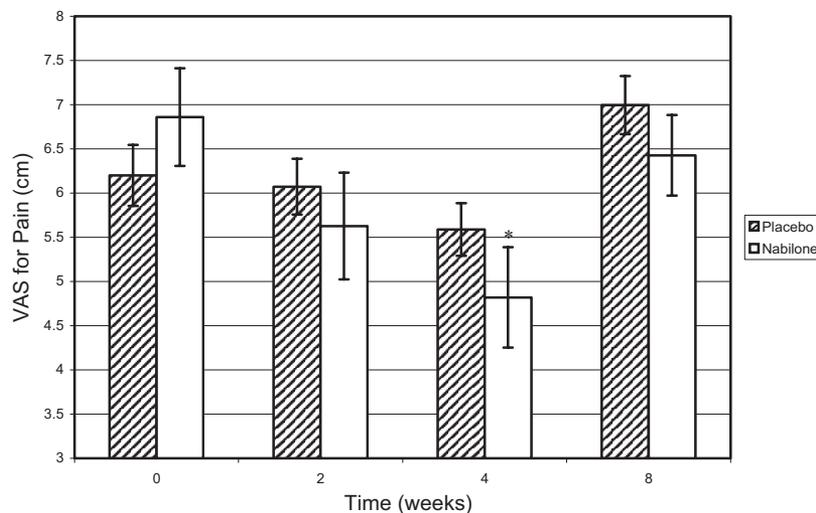


Figure 2. VAS scores, nabilone vs placebo, mean \pm SE. When compared with baseline, nabilone-treated patients had significantly improved VAS scores at 4 weeks (-2.04 , $P < .02^*$).

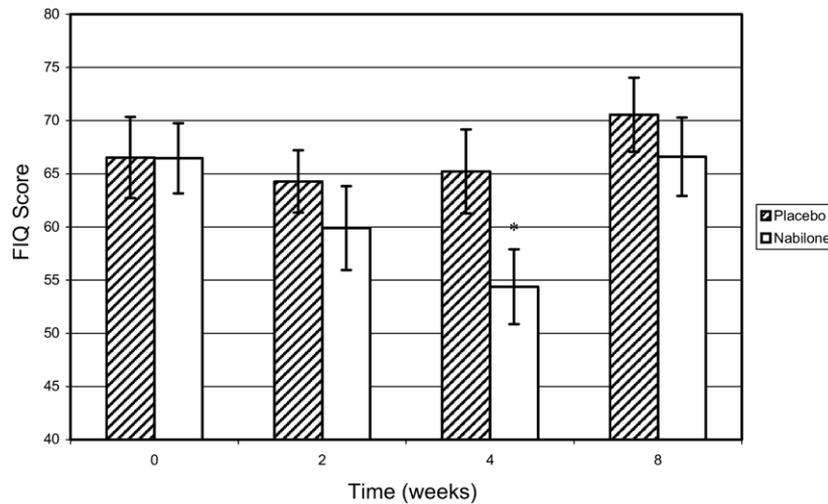


Figure 3. FIQ scores, nabilone vs placebo, mean \pm SE. When compared with baseline, nabilone-treated patients had significantly improved FIQ scores at 4 weeks (-12.07 , $P < .02^*$).

the depression and fatigue scales on the FIQ were not significantly different from baseline values.

Comparing the treatment and placebo groups at 2 weeks of treatment, no significant differences were seen in VAS, number of tender points, tender point pain threshold, or FIQ. Of the 3 separately analyzed questions in the FIQ concerning anxiety, depression, and fatigue, only anxiety was significantly less at the 2-week visit in the nabilone group. The score on the 10-point scale for anxiety decreased in the treatment group at a nabilone dose of 0.5 mg BID (-1.92 , $P < .025$).

At the 4-week visit, statistically significant differences between the treatment and placebo groups were also present. The change from baseline in visual analogue scale pain scores (-1.43 , $P < .05$) (Fig 5), FIQ scores (-10.76 , $P < .01$) (Fig 6), and the FIQ anxiety scale (-2.20 , $P < .01$) (Fig 7) all showed significant improvement when compared with the placebo group.

No significant differences were seen between the treatment and placebo groups after the 4-week washout period at the 8-week visit.

Side effects were more common in the nabilone-treated subjects compared with placebo controls at both 2 and 4 weeks of treatment, (1.58, $P < .02$ and 1.54, $P < .05$), respectively. The frequency of the most common side effects for both groups is listed in Table 2. The most common side effects reported by subjects in the nabilone group include drowsiness (7/15), dry mouth (5/15), vertigo (4/15), and ataxia (3/15). No serious adverse events occurred during the study.

Discussion

Our study was conducted to investigate the possible benefits of the synthetic cannabinoid nabilone on pain reduction and quality of life improvement in patients

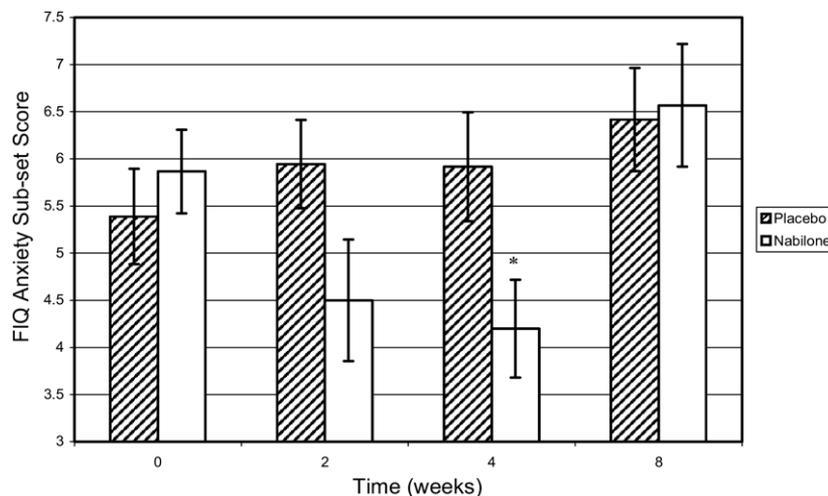


Figure 4. FIQ anxiety subset scores, nabilone vs placebo, mean \pm SE. When compared with baseline, nabilone-treated patients had significantly improved FIQ scores at 4 weeks (-1.67 , $P < .02^*$).

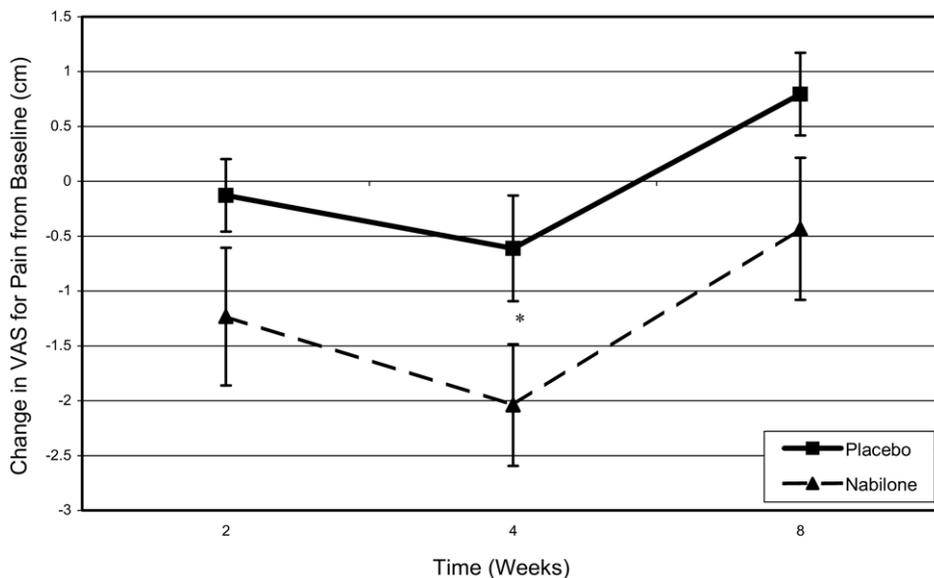


Figure 5. Change in VAS score, nabilone vs placebo, mean ± SE. There was a significant improvement in the change in VAS score in the nabilone group compared with placebo at 4 weeks ($-1.43, P < .05^*$).

with fibromyalgia. Significant reductions in VAS score for pain, FIQ score, and FIQ anxiety score were seen in the treatment group at the 4-week visit. These significant reductions are found both when comparing the treatment group with their baseline values and when comparing the change from baseline to the placebo group at 4 weeks. None of the study participants achieved a total remission of their fibromyalgia symptoms.

Although improvements in VAS and FIQ scores were present after 4 weeks of treatment, there was no significant change in the number of tender points or tender point pain threshold, which is supported by other studies.^{2,23}

Subjects in the placebo group did not obtain any significant benefit in the outcome measures at any time during the study. After a 4-week washout period, out-

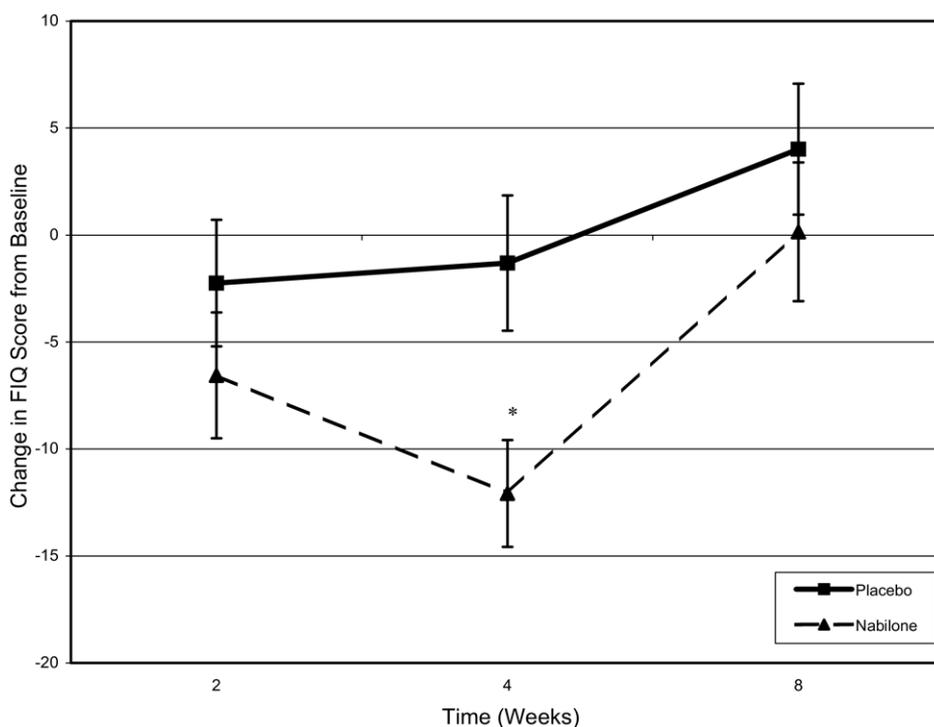


Figure 6. Change in FIQ score, nabilone vs placebo, mean ± SE. There was a significant improvement in the change in FIQ score in the nabilone group compared with placebo at 4 weeks ($-10.76, P < .01^*$).

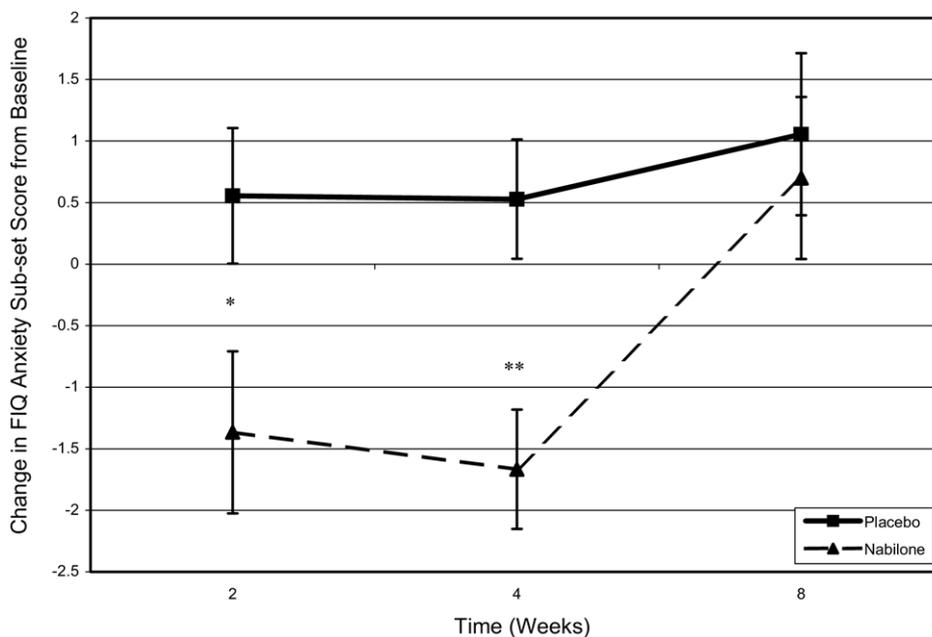


Figure 7. Change in FIQ anxiety subset scores, nabilone vs placebo, mean ± SE. There was a significant improvement in the change in anxiety score in the nabilone group when compared with placebo at 2 and 4 weeks of treatment, with differences of (−1.92, $P < .025^*$) and (−2.20, $P < .01^{**}$), respectively.

come measures were not significantly different from baseline in both groups. Nabilone does not appear to have any lasting benefit in subjects when treatment is discontinued.

Comparing the baseline FIQ scores in our study to some recent studies that used the FIQ, our subjects scored on average 12 to 22 points higher,^{2,5,30} indicating their quality of life was more severely affected by fibromyalgia.²³ As our recruitment practices were similar, the reason for the disparity in the baseline FIQ scores and its effect on our results is unclear.

The significant drop in the VAS (−2.04, $P < .02$) in our treatment group was similar to those of other drug trials, which ranged from 1.2 to 2.2.^{2,5,17} Our finding of a significant drop in the FIQ score (−12.07, $P < .02$) was also similar to other drug trials whose drop in FIQ score ranged from 5.53 to 15.8.^{2,3,5,17,30} Despite the poorer

baseline quality of life of our subjects, they still managed a significant improvement in FIQ scores on par with other studies. This suggests that nabilone is an effective treatment even for those with severe cases of fibromyalgia with marked functional impairment.

Although statistically significant reductions in VAS score for pain, FIQ score, and FIQ anxiety score were observed in this study, the question remains whether these findings are clinically significant? With the current lack of understanding of the pathophysiology of fibromyalgia, and options in its medical management,¹³ the statistically significant benefits obtained in this study are promising and require consideration as an adjunct to the current medical management of fibromyalgia.

The analgesic benefits of cannabinoids in the treatment of acute and chronic pain have already been estab-

Table 2. Side Effects Reported in the Treatment and Placebo Groups at 2 and 4 Weeks

SIDE EFFECT	PLACEBO		NABILONE		SIDE EFFECT	PLACEBO		NABILONE	
	2 WEEK	4 WEEK	2 WEEK	4 WEEK		2 WEEK	4 WEEK	2 WEEK	4 WEEK
Drowsiness	3/20	1/18	7/18	7/15	Blurred vision	1/20	0/18	1/18	0/15
Dry mouth	5/20	1/18	5/18	5/15	Dysphoria	0/20	0/18	2/18	1/15
Vertigo	0/20	0/18	2/18	4/15	Depression	0/20	1/18	0/18	0/15
Ataxia	0/20	1/18	3/18	3/15	Euphoria	0/20	1/18	0/18	1/15
Confusion	0/20	1/18	3/18	2/15	Lightheaded	0/20	0/18	1/18	0/15
Decreased concentration	0/20	1/18	1/18	2/15	Psychological high	1/20	0/18	1/18	0/15
Disassociation	0/20	0/18	2/18	2/15	Nightmares	0/20	1/18	1/18	0/15
Orthostatic hypotension	0/20	1/18	1/18	2/15	Sensory disturbance	0/20	0/18	1/18	1/15
Anorexia	0/20	1/18	1/18	2/15	Tachycardia	0/20	1/18	0/18	0/15
Headache	2/20	3/18	3/18	1/15	Hallucination	0/20	0/18	0/18	0/15

lished,¹⁰ so their benefit in fibromyalgia patients is not surprising. Whether this benefit is secondary to a clinical endocannabinoid deficiency in fibromyalgia patients as has been suggested²⁸ or the synergistic relationship with endogenous opioids,²⁷ it is clear from previous studies that cannabinoids act at many sites along pain transmission pathways.

Other known actions of cannabinoids including inhibition of prostaglandin E-2 synthesis,⁸ its anti-inflammatory effect,¹² experimental increases in β -endorphins,³⁴ and the regulation of substance P and enkephalin mRNA levels in the basal ganglia²² could all contribute to less pain experienced in the nabilone-treated patients.

Anxiety on the FIQ was also decreased in the treatment group at the 4-week visit, which is not exclusive to our study. A trial assessing the effects of tramadol and acetaminophen on patients with fibromyalgia found similar improvements in VAS, FIQ, and anxiety, without significant improvements in depression or fatigue.⁵ Although part of the benefit obtained in pain reduction and quality-of-life improvement in these patients may be secondary to reduced anxiety, other studies have not shown a change in anxiety despite significant functional improvements.³⁰ Further studies with validated scales for anxiety need to be conducted to explore this issue.

Nabilone was generally well tolerated by participants throughout the study. This is reassuring, as it is well known that patients with fibromyalgia are sensitive to most medications and have difficulty tolerating medication side effects.¹⁵ Although there were significantly more side effects per person in the treatment group at 2 and 4 weeks (1.58, $P < .02$ and 1.54, $P < .05$), respectively, no serious adverse effects were seen in the nabilone-treated subjects during the study. Three-quarters of the subjects in the treatment group tolerated the medication well and completed the study. Those who withdrew from the study did so at or before the first follow-up visit at 2 weeks. The reported side effects of nabilone were generally mild, and nabilone did not appear to have adverse interactions with any of the concomitant medications patients were taking, including antidepressants, muscle relaxants, nonsteroidal anti-inflammatories, and opioids. This supports the findings from the previously conducted case series with nabilone and fibromyalgia patients.¹⁸ Slowing the titration of the medication in longer studies may further reduce treatment side effects.

When prescribing nabilone, cost must be taken into consideration. Participants using nabilone at the dose we found to be effective in the study should expect to pay over four thousand dollars for a year's supply of the medication in Canada. Patients must weigh these costs against the potential benefits of pain reduction and improved quality of life. As the medication's cost may be prohibitive to some patients, nabilone probably would not be the first line therapy prescribed to patients with fibromyalgia but should be considered if other treatments have been ineffective.

The current study is not without its limitations. Participants in both groups were allowed to continue any treatments for pain, with the use of nabilone as an adjunctive therapy. Despite the benefit in pain and anxiety reduction and quality of life improvement in the treatment group, it cannot be definitively concluded that the benefit was not a result of the combination of therapies. We thought that allowing both groups to continue their ongoing pain therapies controlled for this variable, and as fibromyalgia patients using complementary therapies ranges in studies from 60 to 90 percent,⁴ the use of nabilone as an adjunct is clinically relevant. Future studies could be done using nabilone as a single agent to determine its effect on pain and quality of life alone.

Given the fluctuating nature of fibromyalgia symptoms,¹⁵ our study was limited by its short duration and limited number of visits. To control for the fluctuating nature of fibromyalgia symptoms a pain journal could be given to subjects; however, this requires more effort on their behalf and may lead to decreased adherence to the protocol.

Subjects were only trialed on nabilone for a total of 4 weeks, of which only the last week of treatment was at 1 mg BID. The long-term effect of nabilone in alleviating pain and improving quality of life in patients with fibromyalgia cannot be determined based on the short duration of the study. As this study was the first randomized, controlled trial to assess the benefits of nabilone in subjects with fibromyalgia, it was reasonable to conduct this study for a shorter duration. Now that our study has shown significant improvements for fibromyalgia patients, future studies should involve a longer duration of the treatment, at a stable dose.

Although anxiety, depression, and fatigue were assessed in this study with single questions on the FIQ, these single questions are not validated scales for the respective symptoms. As the outcome measures in our study focused on pain and quality of life, the VAS for pain and FIQ were the scales used to assess them. Reports exist for^{19,24} and against¹ the incidence of depression and anxiety being higher in the fibromyalgia population, and this area is still up for debate. Chronic fatigue syndrome is associated with fibromyalgia,⁶ and it has been reported that patients with fibromyalgia have less restorative sleep.¹¹ Future studies to evaluate the effect of nabilone on anxiety, depression, and fatigue in patients with fibromyalgia should use validated scales for each.

To our knowledge, this is the first randomized, controlled trial to demonstrate the benefit of nabilone on pain and quality of life in subjects with fibromyalgia. The significant reductions in VAS, FIQ, and anxiety seen in the treatment group, coupled with minimal side effects, suggest that nabilone may be a beneficial, well-tolerated, treatment option in patients with fibromyalgia. Future studies are still necessary to assess the long-term benefit of nabilone on pain and quality of life, and secondary outcome measures such as anxiety, depression, and

fatigue should be further explored with validated assessment tools.

Acknowledgments

The authors would like to thank the RR1 Musculoskeletal Clinic staff at the Rehabilitation Hospital, Nella Chlopecki, the study's nurse coordinator, the Health

Sciences Centre Pharmacy, and the referring physicians for their support in completing this study. The authors would also like to thank Sue Skrabek, B(Ed), BMR (OT), for her editorial assistance and the HSC Medical Staff Council Fellowship Fund for their financial support. A thank you is also extended to the study participants.

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Research

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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

Published: 04 October 2005

Received: 17 August 2005

Harm Reduction Journal 2005, **2**:18 doi:10.1186/1477-7517-2-18

Accepted: 04 October 2005

This article is available from: <http://www.harmreductionjournal.com/content/2/1/18>

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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.

Acknowledgements

Thanks to all the participants for sharing their experiences and to: Andrew Kavasilas for permission to adapt his questionnaire and ongoing support; and Graham Irvine, Franjo Grotenhermen, Laurie Mather, Wayne Hall and Louisa Degenhardt for comments on the questionnaire.

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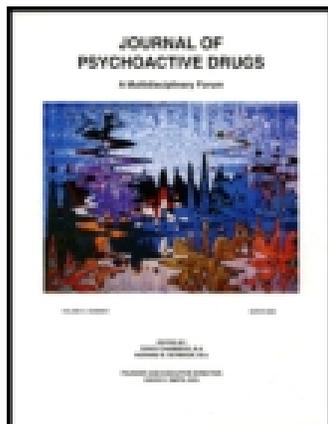


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Journal of Psychoactive Drugs

Publication details, including instructions for authors and subscription information:

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Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics

Craig Reinerman Ph.D.^a, Helen Nunberg M.D. M.P.H.^a, Fran Lanthier M.A.^a & Tom Heddleston M.A.^a

^a Department of Sociology, University of California, Santa Cruz, CA, USA
Published online: 25 Jul 2011.

To cite this article: Craig Reinerman Ph.D., Helen Nunberg M.D. M.P.H., Fran Lanthier M.A. & Tom Heddleston M.A. (2011) Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics, *Journal of Psychoactive Drugs*, 43:2, 128-135, DOI: [10.1080/02791072.2011.587700](https://doi.org/10.1080/02791072.2011.587700)

To link to this article: <http://dx.doi.org/10.1080/02791072.2011.587700>

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Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics[†]

Craig Reinerman, Ph.D.*; Helen Nunberg, M.D., M.P.H.**;
Fran Lanthier, M.A.*** & Tom Heddleston, M.A.***

Abstract—Marijuana is a currently illegal psychoactive drug that many physicians believe has substantial therapeutic uses. The medical literature contains a growing number of studies on cannabinoids as well as case studies and anecdotal reports suggesting therapeutic potential. Fifteen states have passed medical marijuana laws, but little is known about the growing population of patients who use marijuana medicinally. This article reports on a sample of 1,746 patients from a network of nine medical marijuana evaluation clinics in California. Patients completed a standardized medical history form; evaluating physicians completed standardized evaluation forms. From this data we describe patient characteristics, self-reported presenting symptoms, physician evaluations, other treatments tried, other drug use, and medical marijuana use practices. Pain, insomnia, and anxiety were the most common conditions for which evaluating physicians recommended medical marijuana. Shifts in the medical marijuana patient population over time, the need for further research, and the issue of diversion are discussed.

Keywords—anxiety, cannabis therapeutics, insomnia, medical marijuana, pain

Medicinal preparations containing marijuana (cannabis) were widely used in many societies for centuries. Dr. William O'Shaughnessy introduced it as a modern medicine in Europe in 1839. Marijuana was

[†]The authors thank the medical marijuana patient-applicants for providing the data, the RAND Corporation for funding data collection and data set construction, MediCann for administrative support, the Rosenbaum Foundation for financial support for this research, and Lester Grinspoon and anonymous referees for helpful comments. An earlier version of this article was presented at the 59th Annual Meeting of the Society for the Study of Social Problems, San Francisco, August 9, 2009.

*Professor and Chair, Department of Sociology, University of California, Santa Cruz.

**Private practice, Santa Cruz, CA.

***Instructors and PhD candidates, Department of Sociology, University of California, Santa Cruz.

Please address correspondence and reprint requests to Craig Reinerman, Sociology Department, University of California, Santa Cruz, CA 95064; phone: (831) 459-2617, fax: (831) 459-3518, email: craigr@ucsc.edu

prescribed for therapeutic use in American medical practice for a variety of conditions from the mid-nineteenth century into the twentieth. Marijuana was admitted to the *United States Pharmacopoeia* in 1850 and listed in the *National Formulary* and the *US Dispensatory*. Major pharmaceutical companies including Lilly, Burroughs-Wellcome, and Parke-Davis produced cannabis-based therapeutic agents (Brecher et al. 1972).

In 1936, the Federal Bureau of Narcotics advocated a law prohibiting its use, which Congress passed in 1937, against the advice of the American Medical Association (Grinspoon & Bakalar 1993:9–11). This law, along with increased prescribing of aspirin and barbiturates, pushed cannabis out of the *United States Pharmacopoeia* and common medical practice by 1942.

After nonmedical cannabis use spread in the 1960s, the number of Americans reporting lifetime prevalence

increased sharply. Recent estimates from the National Survey on Drug Use and Health show that 102,404,000 Americans have used this drug, 41% of the population aged 12 and over, or about half the adult population (SAMHSA 2010). This widespread use led to a gradual rediscovery of the therapeutic uses of cannabis, albeit largely without physician involvement.

Alongside the spread of nonmedical use, in 1964 scientists determined the precise chemical structure of delta-9 tetrahydrocannabinol (THC), thought to be the most significant psychoactive ingredient in cannabis (Gaoni & Mechoulam 1964). This stimulated research in the clinical pharmacology of cannabinoids. Many physicians in clinical practice also recognized the therapeutic potential of cannabis (Irvine 2006; Charuvastra, Freidmann & Stein 2005), specifically, for example, for pain (Woolridge et al. 2005), as an antiemetic for chemotherapy patients (Doblin & Kleiman 1991), or for symptoms of AIDS (Abrams et al. 2003). More recently a broader medical literature documenting the therapeutic properties of endogenous cannabinoids has developed (e.g., Nicoll & Alger 2004; Lehmann et al. 2002; Hall, Degenhart & Currow 2001). Numerous case reports in the medical literature also have suggested that cannabis has therapeutic potential for a variety of conditions. But rigorous experimental research that might determine more precisely the therapeutic efficacy of cannabis for specific conditions has been blocked by the Drug Enforcement Administration (see Zeese 1999; *Alliance for Cannabis Therapeutics v. Drug Enforcement Administration* 1994).

This combination of increasing therapeutic use and federal government opposition ultimately led to passage of new state laws providing for the medical use of cannabis upon physician recommendation. Since 1996, 15 U.S. states and the District of Columbia have passed such laws: California, Alaska, Oregon, Washington, Nevada, Colorado, Maine, Montana, Michigan, and Washington, DC by ballot initiative; Rhode Island, New Mexico, Vermont, Hawaii, and New Jersey by state legislation.

The first of these laws was California's Proposition 215, the Compassionate Use Act, passed in 1996 (*San Francisco Chronicle* 1996). This act made it legal under state law for patients to possess and use cannabis if recommended by their physicians. Numerous medical and scientific associations endorsed medical use of cannabis and/or supported further research into its therapeutic potential. These included the American College of Physicians (2008), the American Public Health Association (1995), the British Medical Association (1997), the Canadian Medical Association (2005), and the Institute of Medicine of the National Academy of Sciences (1999).

Such elections and endorsements notwithstanding, the Bush Administration's Office of National Drug Control Policy threatened to revoke the licenses of physicians who recommended cannabis to patients. One physician

challenged this policy and the U.S. Court of Appeals ruled (in *Conant v. Walters*) in 2002 that it unconstitutionally infringed physicians' First Amendment rights to freedom of speech with their patients (McCarthy 2004). Subsequent legislation and case law have left medical marijuana (MM) patients and their physicians in legal limbo:

- In 2003, the California legislature passed SB 420 to provide specific implementation guidelines for Proposition 215, including how counties should handle MM patient ID cards.
- Most drug law enforcement is done by local police who enforce state, not federal, drug laws. In 2005, The California Attorney General ruled that Proposition 215 is the legitimate will of the voters and is therefore valid under the California Constitution for purposes of *state* law enforcement. He advised the Highway Patrol and other state law enforcement agencies that under California law MM patients were legally entitled to possess and use cannabis for therapeutic purposes (Hoge 2005).
- In 2006, Bush administration Attorney General Gonzales sought to invalidate state MM laws, and the U.S. Supreme Court ruled (*Gonzales v. Raich* 2006) that the Compassionate Use Act—its legitimate electoral provenance notwithstanding—neither supersedes nor invalidates federal laws that prohibit marijuana use (see Mikos 2009 for a legal analysis of the states' neglected power to legalize behavior that is criminalized under federal law).
- In 2008 the Supreme Court denied without comment an appeal by two California counties that had refused to implement Proposition 215 (*County of San Diego v. San Diego NORML* 2008), thereby letting stand a lower court ruling that upheld SB 420's provisions regarding counties issuing MM identification cards.
- In 2009, Attorney General Eric Holder issued a policy stating that federal drug control agencies would no longer raid MM dispensaries if they operated within state and local laws (Moore 2009).
- That policy notwithstanding, the DEA has continued to raid MM dispensaries in California into 2011 (e.g., Blankstein 2009).

Within this grey area between conflicting state and federal laws, the number of patients who have received recommendations for medical marijuana from physicians has continued to grow, albeit by how much remains unknown. Over 1,000 MM dispensaries, delivery services, and cooperatives are said to be operating in California to meet the demand (NORML 2007). A rough estimate of the number of MM patients in California can be extrapolated from Oregon figures. Unlike California's Compassionate Use Act, Oregon's MM law set up an Oregon Medical Marijuana Program that requires centralized record keeping. As of July, 2009, some 2,983 Oregon-licensed physicians had approved 20,307 applications for MM (Oregon

Department of Human Services 2008). The population of California is 9.7 times that of Oregon (U.S. Census 2007), which yields a crude estimate of 196,978 MM patients in California. This is likely an underestimate because the California statute affords greater latitude to physicians regarding the conditions for which they can recommend MM (“... any other illness for which marijuana provides relief”). Americans for Safe Access (2008), a MM patient advocacy group, has estimated that there are well over 200,000 physician-sanctioned MM patients in California.

Despite their growing numbers, however, the ambiguous legal status of MM patients renders them a half-hidden population whose characteristics are not well documented, with the partial exception of the San Francisco Bay Area (O’Connell & Bou-Matar 2007; Reiman 2007a). Medical marijuana will likely continue to be a contentious issue, but across fifteen states and the District of Columbia several hundred thousand people are using marijuana as a medicine recommended by physicians, and yet little is known about them as a patient population.

We intend this study as a modest contribution toward filling this gap. It presents data on the demographic characteristics, presenting symptoms, physician evaluations, conventional treatments tried, and MM use practices of patients from a network of MM assessment clinics in California.

METHODS

These data were drawn from 1,746 consecutive admissions to nine MM assessment clinics operating in California in July, August, and September 2006. These assessment clinics are not dispensaries and are not connected to dispensaries. They were located throughout the state—in the north and south, coast and central valley, and large and small cities: Modesto, Oakland, Sacramento, Hollywood, San Diego, Santa Cruz, Ukiah, San Francisco, and Santa Rosa. They charged \$100 to \$125 for an assessment. At the time our sample was drawn, these assessment clinics had evaluated over 54,000 MM patients. Without a comprehensive patient database or representative household surveys, there is no way to determine precisely how representative this sample is of the overall population of MM patients. Moreover, there is a large albeit unknown number of people who use marijuana medicinally but who have not sought physician recommendations or official patient ID cards, perhaps because of the expense of the assessment.¹

Evaluating physicians interviewed potential patients and evaluated their patient medical histories for purposes of recommending MM and issuing patient identification cards under the Compassionate Use Act and SB 420. The evaluation instruments were (1) a basic patient-administered medical history questionnaire covering demographics, presenting symptoms or conditions, brief medical history,

conventional and alternative medical treatments tried, drug use history, and MM use practices; and (2) a physician evaluation form using International Classification of Diseases codes (ICD-9). Each patient received and signed an extensive informed consent form noting confidentiality, which was approved by the clinics’ IRB.

Most prior studies of MM patients are based on small, symptom-specific samples. Initially, the population of MM patients in the San Francisco Bay Area were people with HIV/AIDS and cancer (e.g., Harris, Mendelson & Jones 1998). Later, physicians began to recommend cannabis to patients with chronic pain, mood disorders and other psychiatric conditions (Gieringer 2002). The data reported here describe what is among the largest and most symptomatically and demographically diverse samples of medical cannabis patients to date (cf., O’Connell & Bou-Matar 2007).

RESULTS

As Table 1 indicates, the MM patients are three-fourths male and three-fifths White. Compared to the US Census of California, the patients in this sample are on average somewhat younger, report slightly more years of formal education, and are more often employed. The comparison also indicates that women, Latinos, and Asian Americans are underrepresented. Given the limitations of our data, we can offer only informed speculation as to why.

The underrepresentation of women may be in part an epidemiological artifact of the gender distribution of certain kinds of injuries (e.g., workplace, sports, and motorcycle accidents). It may also have to do with the double stigma women face in seeking MM—for using an illicit drug and for violating gender-specific norms against illegal behavior in general. Moreover, as with alcohol use, pregnant women and women considering pregnancy are likely to have health concerns and many may fear that MM could put them in jeopardy if discovered by child protection agencies.

Given the high poverty rate among Latinos and their concentration in the manual labor end of the occupational structure, Latinos are exposed to equal or greater risks of work-related injuries and to no less epidemiologic risk of other conditions for which MM is sometimes used. It seems likely that their under-representation has to do with the undocumented status of many Latinos in California. The undocumented often avoid contact with government agencies for fear of apprehension by law enforcement, for beyond arrest and incarceration this carries the risk of deportation. Such fears reduce the likelihood of Latinos accessing health care in general and MM in particular. Asian Americans are also underrepresented, but this may be because they have lower prevalence of marijuana use than other racial/ethnic groups and/or because they have their own venerable traditions of herbal medicine.

TABLE 1
Demographic Characteristics of California Medical Marijuana Patients Compared to California Census 2000, Age 18 and Over {n = 1746}

	MM Patients	U.S. Census 2000 – California
Female	27.1%	50.7%
Male	72.9%	49.3%
White	61.5%	59.5%
Latino	14.4%	32.4%
African American	11.8%	6.7%
Native American	4.5%	1.0%
Asian/Pacific Islander	4.2%	11.2%
Other	4.3%	*
18–24 Years Old	17.9%	~17.1%
25–34 ”	27.5%	15.4%
35–44 ”	21.3%	16.2%
45–54 ”	20.4%	12.8%
55> ”	12.6%	18.4%
<High School	8.8%	*
High School Graduate	42.2%	*
Some College	27.1%	*
College Graduate>	23.8%	*
Employed	64.8%	57.5%
Health Insurance	73.4%	*

*Data not available in California Census.

African-Americans, conversely, are over-represented in this sample. This does not appear to stem from their prevalence of marijuana use, for representative national surveys show that Blacks generally do not have significantly higher prevalence of marijuana use than Whites (SAMHSA 2005). African-Americans may be more likely to seek MM for any of several reasons: because they are disproportionately poor, more often lack health insurance, are significantly less likely to be prescribed other medication for pain (Pletcher et al. 2008) or to receive treatment for cancer (Gross et al. 2008), and because African-Americans are a growing proportion of HIV/AIDS cases. Some of these same reasons may help to explain why Native Americans are also overrepresented, although their proportion of both this sample and the general population is too small to judge representativeness accurately.

In their medical history questionnaires, patients were asked “Which of the following best describe the therapeutic benefit you receive from medicinal cannabis? (Check the most important).” Patients typically reported more than one therapeutic benefit (mean = 3). Early studies showed most patients used MM to relieve symptoms of HIV/AIDS (Woolridge et al. 2005) or cancer, and it is likely that the majority of patients in our sample who reported “nausea” were cancer patients receiving chemotherapy. However, Table 2 suggests that cancer and AIDS patients are now a

TABLE 2
Patient Self-Reports of Therapeutic Benefits from Medicinal Marijuana*

	Percent
To Relieve:	
Pain	82.6
Muscle Spasms	41.1
Headaches	40.7
Anxiety	37.8
Nausea/Vomiting	27.7
Depression	26.1
Cramps	19.0
Panic Attacks	16.9
Diarrhea	5.0
Itching	2.8
To Improve:	
Sleep	70.7
Relaxation	55.1
Appetite	37.7
Concentration/Focus	22.9
Energy	15.9
To Prevent:	
Medication Side Effects	22.5
Anger	22.4
Involuntary Movements	6.2
Seizures	3.2
As Substitute for:	
Prescription Medication	50.9
Alcohol	13.0

*N = 1,745; patients could report more than one benefit in more than one category.

significantly smaller proportion of the total (e.g., “to relieve nausea/vomiting” 27.7%, “to improve appetite” 37.7%) and that the MM patient population has become more diverse since the Compassionate Use Act was passed in 1996 (cf. Ware, Adams & Guy 2005, on MM use in the UK, and Grotenherman 2002 on MM use in Germany).

Instead, relief of pain, muscle spasms, headache, and anxiety, as well as to improve sleep and relaxation were the most common reasons patients cited for using MM. Chronic pain also topped the list of maladies for which MM was used in another California clinical sample (Reiman 2007b).

Table 3 shows the ICD-9 diagnostic codes most frequently recorded by evaluating physicians. Pain from back and neck injuries was the most frequently coded. This appears consistent with a nationally representative Medical Expenditure Panel Survey, which found a 19.3% increase in the prevalence of spine problems between 1997 and 2005 (Martin et al. 2008). Back and neck pain was followed in frequency by sleep disorders (also increasing), anxiety/depression, muscle spasms, and arthritis. Fully half of this sample reported using MM as a substitute

TABLE 3
Conditions Most Frequently Recorded by Physicians As Reasons for Approving Medical Marijuana Patient Identification Cards*

	Percent	ICD-9 Codes
Back/Spine/Neck Pain	30.6%	[722.1–724.2]
Sleep Disorders	15.7%	[307.42, 327.0]
Anxiety/Depression	13.0%	[300.0, 311.0]
Muscle Spasms	9.5%	[728.85]
Arthritis	8.5%	[715.0, 721.2, 721.2]
Injuries (Knee, Ankle, Foot)	4.5%	[959.7]
Joint Disease/Disorders	4.4%	[716.1–719.49]
Narcolepsy	3.7%	[347.0]
Nausea	3.4%	[787.02]
Inflammation (Spine, Nerve)	2.9%	[724.4]
Headaches/Migraines	2.7%	[784.0, 346.0, 346.2]
Eating Disorders	1.1%	[783.0]

*N = 1746; some patients reported multiple symptoms and/or conditions.

TABLE 4
Other Treatment Modalities Tried for the Medical Condition(s) for Which Patients Seek Medical Marijuana*

	%	N
Prescription Medication	79.3%	1383
Physical Therapy	48.7	850
Chiropractic	36.3	633
Surgery	22.3	389
Counseling	21.0	366
Acupuncture	19.4	338
Therapeutic Injection	15.4	269
Homeopathy	12.0	209
Other Types of Treatment	11.9	208

*N = 1746; patients could report multiple other treatments.

for prescription drugs, consistent with other studies (e.g., Reiman 2007a).

Table 4 indicates that the MM patients in the sample had tried a variety of other treatments, conventional and alternative, for the conditions for which they were seeking a MM identification card. Four in five (79.3%) reported having tried other medications prescribed by their physicians (almost half were opiates); about half (48.7%) had tried physical therapy; over a third (36.3%) had tried chiropractic; nearly one-fourth (22.3%) reported having had surgery for their condition.

Table 5 compares patient responses to the drug use questions to those in the 2006 National Survey on Drug Use and Health (SAMHSA 2007). Prevalence of tobacco

TABLE 5
Medical Marijuana Patients' Self-Reported Current Nonmedical Drug Use, Compared to 2006 National Survey on Drug Use And Health (SAMHSA 2007)

	MM Patients	NSDUH*
Tobacco	29.4%	25.0%
Alcohol	47.5	61.9
Cocaine	0.3	1.9
Methamphetamine	0.4	0.5
Heroin	0.1	0.3
Other Opiates	1.2	**

Note: Participants were asked "Do you currently use . . ."; answers are percent responding "yes." N = 1745; patients could report more than one drug. Of smokers, 65.5% used ten or less cigarettes/day; of drinkers, 58.7% used <= one or less drinks/day.

*NSDUH figures for "past month" prevalence used as a proxy for "current use".

**Data not available in comparable form.

use was somewhat higher than in the general population, but prevalence of alcohol use was significantly lower. Many patients reported that they valued MM because it allowed them to reduce their alcohol use. It is possible that self-reports on a self-administered instrument will underestimate illicit drug use, particularly if patients felt that admitting illicit drug use could reduce their chances of obtaining a MM identification card. Rigorous assessments of the reliability of such data must await further research, but limitations aside, these data suggest low prevalence of other illicit drug use among MM patients. While it is true that the great majority of our respondents had used marijuana recreationally, in response to a separate question over two-fifths (41.2%) reported that they had *not* been using it recreationally prior to trying it for medicinal purposes.

Table 6 presents data on patients' medical marijuana use practices. Amounts used per week varied from three grams or less (40.1%) to seven or more grams (23.3%). Two-thirds (67%) reported using MM daily while one-fourth (26%) reported using less than once a week. Half (52.9%) reported using one or two times per day while one in ten (10%) reported using three or more times per day. Patients consumed MM primarily in the evenings (52.3%) or prior to sleep (56.1%). More than two in five (42.3%) reported that when they used depended on their medical symptoms. Patients ingested MM predominantly by smoking (86.1%), although one-fourth (24.4%) reported ingesting orally and nearly a fourth (21.8%) reported using a vaporizer. These latter figures suggest that at least some of the time, many MM patients are choosing modes of ingestion that reduce the perceived risk of harms from smoking (Tan et al. 2009; Hashibe et al. 2006).

TABLE 6
Medical Marijuana Use Practices

Frequency of Medical Marijuana Use (N = 1583)*	
Daily	67.0% (1065)
<Once A Week	26.0% (409)
<Once A Month	7.0% (109)
On Days Used, Frequency per Day (N = 1574)	
1 To 2 Times Per Day	52.9% (833)
2 To 3 Times Per Day	29.0% (457)
>3 Times Per Day	10.0% (284)
Time Of Day Typically Used (N = 1745)	
Prior To Sleep	56.1% (979)
Evenings	52.3% (913)
Depends on Symptoms	42.3% (739)
Mornings	25.7% (448)
Afternoons	20.1% (350)
After Work	12.4% (217)
Middle of the Night	6.5% (114)
All Day	5.3% (93)
Mode of Ingestion (N = 1745)	
Smoke	86.1% (1503)
Oral Ingestion	24.4% (426)
Vapor	21.8% (380)
Topical	2.8% (49)
Amount Used per Week (N = 1431)	
0–3 Grams	40.1% (574)
4–7 Grams	36.5% (523)
>7 Grams	23.3% (334)

*Total n = 1745, but N's vary across questions because patients could choose more than one response and because not all responded to each question.

DISCUSSION

Rediscovery of Medicinal Utility and Diversifying Patient Population

Compared to earlier studies of MM patients, these data suggest that the patient population has evolved from mostly HIV/AIDS and cancer patients to a significantly more diverse array. The diffusion of marijuana as a medicine may have been slower than that of other medicines in conventional clinical practice because the flow of information from physician to patient is impeded by MM's ambiguous legal status. Thus, information about the potential therapeutic utility of cannabis is spread mostly via word of mouth and other informal means. This suggests that the patient population is likely to continue evolving as new patients and physicians discover the therapeutic uses of cannabis. Ironically, this trend toward increasing therapeutic uses is bringing marijuana back to the position it held in the U.S. Pharmacopeia prior to its prohibition in 1937.

Further Research

Like other medicines, marijuana's therapeutic efficacy varies across conditions and patient groups. This variation seems more likely when supplies remain illicit because standardized dosages or other quality controls are more difficult to achieve. To gain maximum therapeutic potential across the growing range of conditions for which MM is being recommended, more systematic research is needed. Longitudinal, case control, and double-blind studies are required to rigorously assess marijuana's therapeutic efficacy for specific patient groups, conditions, and diseases. With regard to shifts in the patient population, it also would be very useful to have follow-up studies of patients accessing the assessment clinics in our sample and others drawn from similar assessment clinics.

Diversion

Critics have argued that some MM patients are "gaming the system" to get marijuana for nonmedical use. Neither our data nor any other data we are aware of allow any clear-cut, empirical estimate of the scale of such diversion. Given the widespread nonmedical use marijuana in the general population (102,404,000 Americans report lifetime prevalence; see SAMHSA 2010) and the risk of arrest (847,864 Americans were arrested for marijuana offenses in 2008, 754,224 or 88.96% of them for possession alone; FBI 2009), it seems likely that at least some MM patients use MM dispensaries as sources of supply for nonmedical use.

Defining and measuring such diversion, however, is complicated at best. Given the high prevalence of nonmedical use, it is not surprising that most MM patients in our sample reported having used it recreationally before using it therapeutically. But as noted above, two-fifths had *not* been using marijuana recreationally prior to trying it for medicinal purposes. Their self-reported rates of other illicit drug use are slightly lower than those found among the general population, and their levels of educational attainment and rate of employment are comparable to the California population. Our data have clear limitations, but they contain no obvious signs that MM patients differ from the general population.

Nor is drug diversion unique to medical marijuana. A significant albeit unknown proportion of other patients obtain prescriptions for numerous drugs through legal medical channels that they then use for nonmedical purposes, for example, Valium and other benzodiazepines (Haafkens 1997), Ritalin and other stimulants prescribed for ADHD, and Oxycontin and other opiates prescribed for pain.

The diversion issue will likely become more important as the line between medical and nonmedical drug use is increasingly blurred (Murray, Gaylin & Macklin 1984). Beyond the spread of MM, Prozac and other SSRI-type antidepressants, for example, are often prescribed

for patients who do not meet DSM criteria for clinical depression but who simply feel better when taking it. Such “cosmetic psychopharmacology” (Kramer 1993) is likely to grow as new psychiatric medications come to market. The line between medical and nonmedical drug use has also been blurred by performance enhancing drugs such as steroids, so-called “smart drugs” that combine vitamins with psychoactive ingredients, and herbal remedies like *ma huang* (ephedra) available in health food stores (Burros & Jay 1996).

These examples suggest that despite the best intentions of physicians and law makers, much drug use does not fit into two neat boxes, medical and nonmedical, but rather exists on a continuum where one shades into the other as

patients’ purposes shift to suit situational exigencies in their health and their daily lives. It is not clear where a border line between medical and nonmedical marijuana or other drug use might be drawn nor how it might be effectively policed (see Reinarman & Levine 1997: 334–44).

NOTE

1. We are grateful to one anonymous reviewer for pointing out that the cost of these assessments may well have prevented some potential MM patients—including many impoverished HIV/AIDS patients—from obtaining ID cards, which may have affected the demographics of this sample.

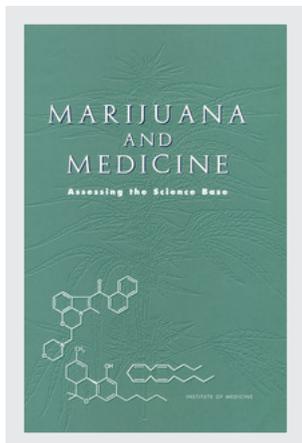
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CONTRIBUTORS

Janet E. Joy, Stanley J. Watson, Jr., and John A. Benson, Jr., Editors;
Institute of Medicine

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Institute of Medicine 1999. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: The National Academies Press.
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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

INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C.

NATIONAL ACADEMY PRESS • 2101 Constitution Avenue, N.W. • Washington, D.C. 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The principal investigators responsible for the report were chosen for their special competences and with regard for appropriate balance.

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This study was supported under Contract No. DC7C02 from the Executive Office of the President, Office of National Drug Control Policy.

Library of Congress Cataloging-in-Publication Data

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, Institute of Medicine.

p. cm.

Includes bibliographical references and index.

ISBN 0-309-07155-0 (hardcover)

1. Marijuana—Therapeutic use. 2. Cannabinoids—Therapeutic use.

I. Joy, Janet E. (Janet Elizabeth), 1953- II. Watson, Stanley J., 1943- III. Benson, John A. IV. Institute of Medicine (U.S.).

Division of Neuroscience and Behavioral Health.

RM666.C266 M365 1999

615'.32345—dc21

99-6484

Additional copies of this report are available for sale from the National Academy Press, 2101 Constitution Avenue, N.W., Lock Box 285, Washington, D.C. 20055. Call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP's online bookstore at www.nap.edu.

The full text of this report is available online at www.nap.edu.

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Printed in the United States of America

Cover: Illustration from *Marijuana Botany* by Robert Connell Clarke, Ronin Publishing, 1981.

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).

Jane Sanville, project officer for the study sponsor, was consistently helpful during the many negotiations and discussion held throughout the study process. Many Institute of Medicine staff members provided greatly appreciated administrative, research, and intellectual support during the study. Robert Cook-Deegan, Marilyn Field, Constance Pechura, Daniel Quinn, and Michael Stoto provided thoughtful and insightful comments on draft sections of the report. Others provided advice and consultation on many other aspects of the study process: Clyde Behney, Susan Fourt, Carolyn Fulco, Carlos Gabriel, Linda Kilroy, Catharyn Liverman, Dev Mani, and Kathleen Stratton. As project assistant throughout the study, Amelia Mathis was tireless, gracious, and reliable.

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.

Contents

EXECUTIVE SUMMARY	1
1 INTRODUCTION	13
How This Study Was Conducted, 15	
Marijuana Today, 16	
Marijuana and Medicine, 19	
Who Uses Medical Marijuana? 20	
Cannabis and the Cannabinoids, 24	
Organization of the Report, 30	
2 CANNABINOIDS AND ANIMAL PHYSIOLOGY	33
Introduction, 33	
Cannabinoid Receptors, 39	
The Endogenous Cannabinoid System, 43	
Sites of Action, 48	
Cannabinoid Receptors and Brain Functions, 51	
Chronic Effects of THC, 56	
Cannabinoids and the Immune System, 59	
Conclusions and Recommendations, 69	
3 FIRST, DO NO HARM: CONSEQUENCES OF MARIJUANA USE AND ABUSE	83
The Marijuana “High,” 83	
Drug Dynamics, 84	

Marijuana Use and Dependence, 92	
Link Between Medical Use and Drug Abuse, 101	
Psychological Harms, 104	
Physiological Harms: Tissue and Organ Damage, 109	
Summary and Conclusions, 125	
4 THE MEDICAL VALUE OF MARIJUANA AND RELATED SUBSTANCES	137
Standards for Evaluating Clinical Trials, 138	
Analgesia, 139	
Nausea and Vomiting, 145	
Wasting Syndrome and Appetite Stimulation, 154	
Neurological Disorders, 159	
Glaucoma, 173	
Summary, 177	
Other Reports on Marijuana as Medicine, 180	
5 DEVELOPMENT OF CANNABINOID DRUGS	193
Federal Drug Development Policy, 194	
Development and Marketing of Marinol, 202	
Market Outlook for Cannabinoids, 208	
Regulation of and Market Outlook for Marijuana, 213	
Conclusions, 218	
APPENDIXES	
A Individuals and Organizations That Spoke or Wrote to the Institute of Medicine About Marijuana and Medicine	225
B Workshop Agendas	232
C Scheduling Definitions	240
D Statement of Task	242
E Recommendations Made in Recent Reports on the Medical Use of Marijuana	244
F Rescheduling Criteria	256
INDEX	259

List of Tables and Figures

TABLES

- 1.1 Self-Reported Disorders Treated with Marijuana by Members of San Francisco Cannabis Cultivators Club, 21
- 1.2 Self-Reported Disorders Treated with Marijuana by Members of Los Angeles Cannabis Resource Center (LACRC), According to Center Staff, 22
- 1.3 Summary of Reports to IOM Study Team by 43 Individuals, 23
- 1.4 Primary Symptoms of 43 Individuals Who Reported to IOM Study Team, 24
- 1.5 Cannabinoids Identified in Marijuana, 25

- 2.1 Landmark Discoveries Since the 1982 IOM Report, 34
- 2.2 Compounds That Bind to Cannabinoid Receptors, 44
- 2.3 Comparison of Cannabinoid Receptor Agonists, 46
- 2.4 Cellular Processes That Can Be Targeted for Drug Development, 48
- 2.5 Brain Regions in Which Cannabinoid Receptors Are Abundant, 49
- 2.6 Cannabinoid Receptors, 51
- 2.7 Effects of Cannabinoids on the Immune System, 60
- 2.8 Historical Comparisons Between Cannabinoids and Opiates, 69

- 3.1 Psychoactive Doses of THC in Humans, 85
- 3.2 Drug Withdrawal Symptoms, 90
- 3.3 Factors That Are Correlated with Drug Dependence, 94

- 3.4 Prevalence of Drug Use and Dependence in the General Population, 95
- 3.5 Relative Prevalence of Diagnoses of Psychiatric Disorders Associated with Drug Use Among Children, 96
- 3.6 Effect of Decriminalization on Marijuana Use in Emergency Room (ER) Cases, 103

- 4.1 Studies on the Effects of Marijuana and Cannabinoids in Multiple Sclerosis, 163
- 4.2 Classes of Antispasticity Drugs, 164
- 4.3 Drugs Used to Treat Movement Disorders, 168
- 4.4 Clinical Trials of Cannabidiol (CBD) in Epileptics, 171
- 4.5 Anticonvulsant Drugs for Various Types of Seizures, 172
- 4.6 Classes of Drugs Used to Treat Glaucoma, 176

- 5.1 Cannabinoids and Related Compounds Commonly Used in Research, 201
- 5.2 Cannabinoids Under Development for Human Use, 209

FIGURES

- 1.1 Cannabinoid biosynthesis, 26

- 2.1 Diagram of neuron with synapse, 38
- 2.2 Cannabinoid receptors, 40
- 2.3 Cannabinoid agonists trigger a series of reactions within cells, 41
- 2.4 Chemical structures of selected cannabinoid agonists, 45
- 2.5 Locations of brain regions in which cannabinoid receptors are abundant, 50
- 2.6 Diagrams showing motor regions of the brain, 52

- 3.1 Age distribution of marijuana users among the general population, 93

- 4.1 Emesis-stimulating pathways, 146
- 4.2 Effect of nabilone on multiple sclerosis symptoms, 162

- 5.1 Stages of clinical testing, 196

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

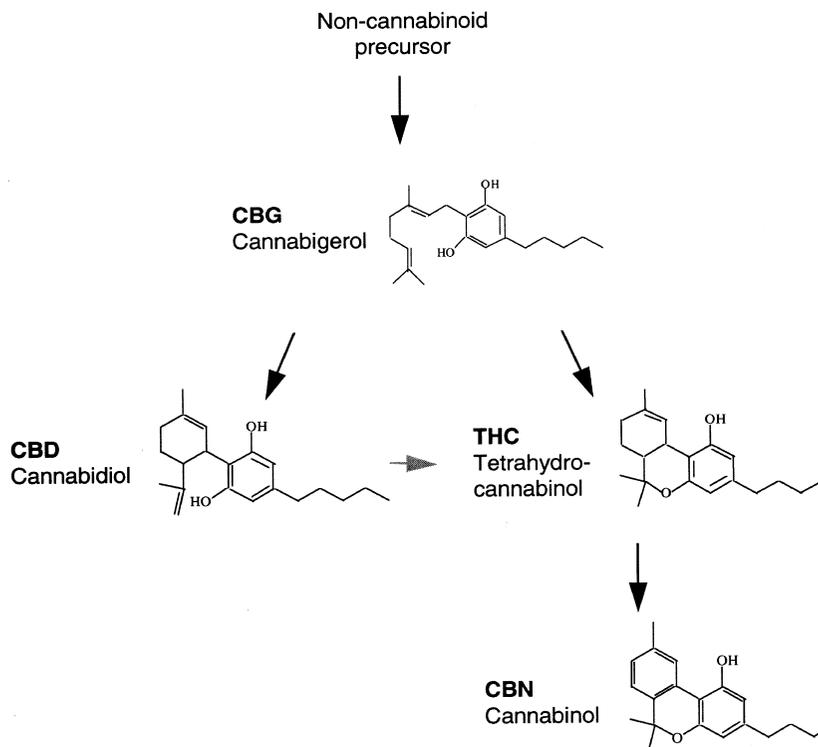


FIGURE 1.1 Cannabinoid biosynthesis. Arrows indicate cannabinoid biosynthesis pathway; dark arrows indicate established pathways; the light gray arrow indicates a probable but not well-established pathway (R. Mechoulam, Hebrew University, personal communication, 1999).¹¹ The great majority of studies 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.

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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

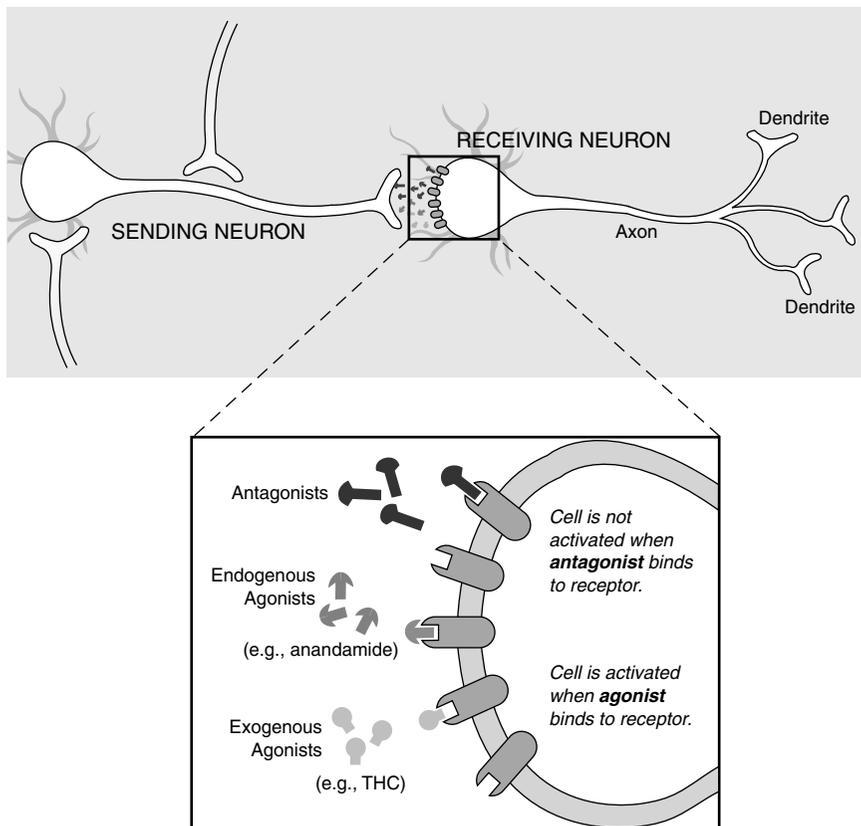


FIGURE 2.1 Diagram of neuron with synapse. Individual nerve cells, or neurons, both send and receive cellular signals to and from neighboring neurons, but for the purposes of this diagram only one activity is indicated for each cell. Neurotransmitter molecules are released from the neuron terminal and 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.

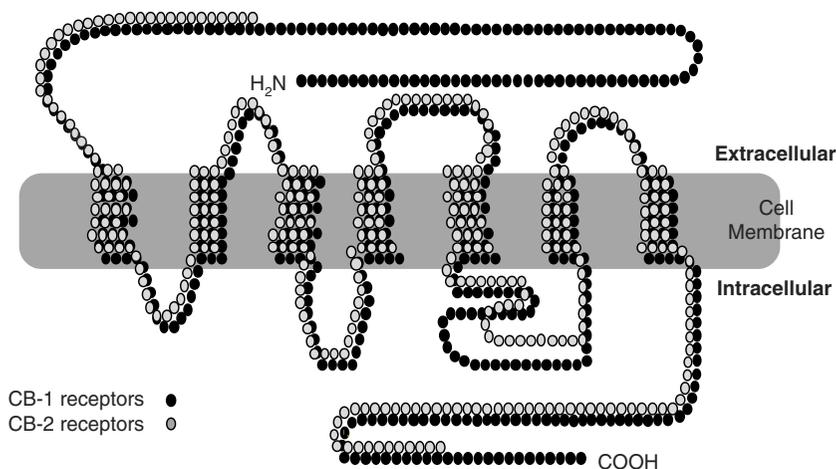


FIGURE 2.2 Cannabinoid receptors. Receptors are proteins, and proteins are made up of strings of amino acids. Each circle in the diagram represents one amino acid. The shaded bar represents the cell membrane, which like all cell membranes in animals is composed largely of phospholipids. Like many receptors, 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-

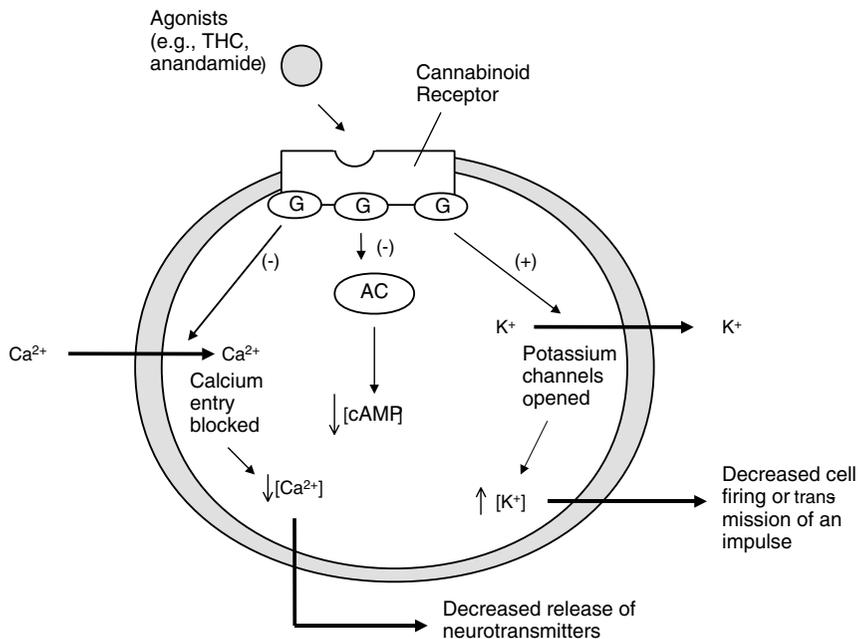


FIGURE 2.3 Cannabinoid agonists trigger a series of reactions within cells. Cannabinoid receptors are embedded in the cell membrane, where they are coupled to G proteins (G) and the enzyme adenylyl cyclase (AC). Receptors are activated when they bind to ligands, such as anandamide or THC in this case. 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

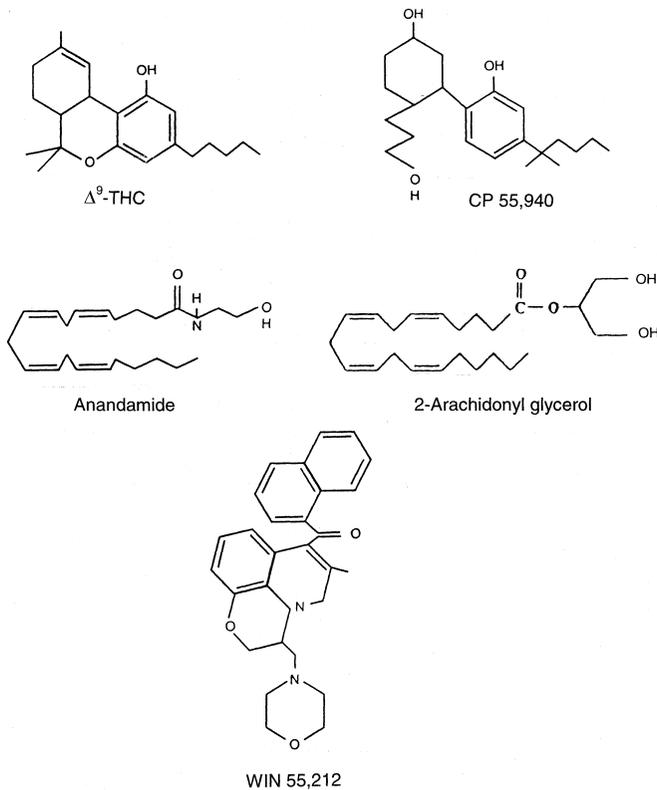


FIGURE 2.4 Chemical structures of selected cannabinoid agonists or molecules that bind to and activate cannabinoid receptors. **THC** is the primary psychoactive molecule found in marijuana. **CP 55,940** is a THC analogue; that is, its chemical structure is related to THC. **Anandamide** and **2-arachidonyl 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

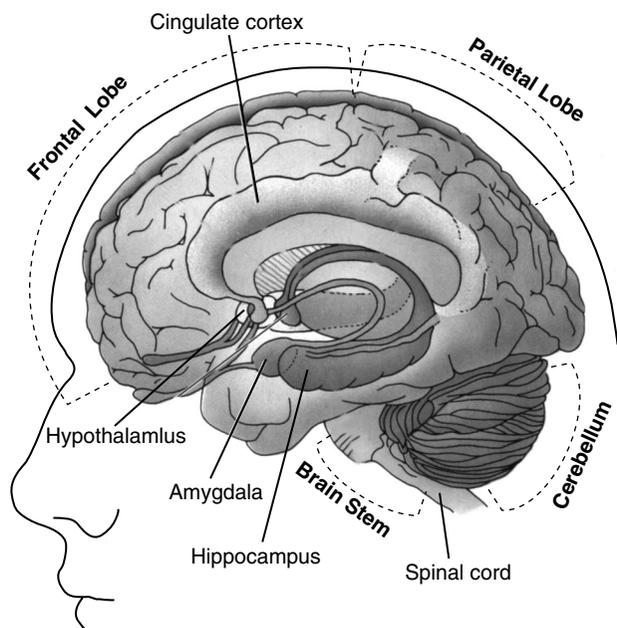


FIGURE 2.5 Locations of brain regions in which cannabinoid receptors are abundant. See Table 2.5 for a summary of functions associated with those regions.

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-

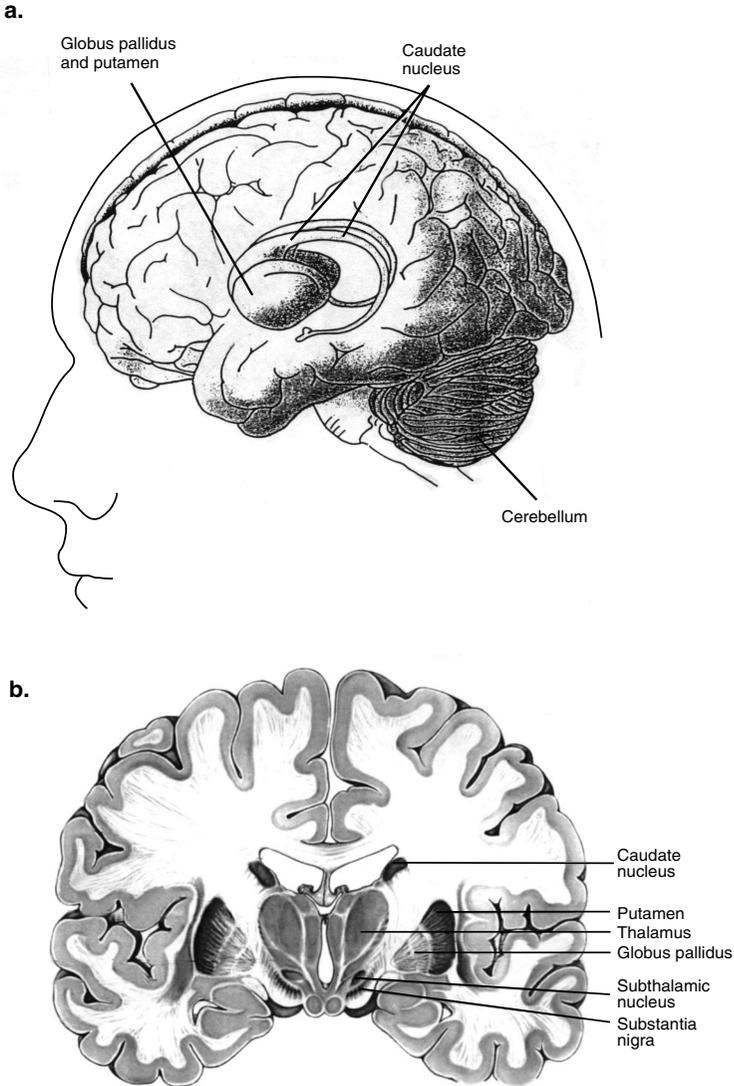


FIGURE 2.6 Diagrams showing motor regions of the brain. Basal ganglia are a group of three brain regions, or nuclei—**caudate**, **putamen**, and **globus pallidus**. Figure 2.6a is a three-dimensional view showing the location of those nuclei in the brain. Figure 2.6b shows those structures in a vertical 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 μ M
THC, 2-AG	Lymphocytes and splenocytes	0.1–25 μ M
Anandamide	Splenocytes <i>in vitro</i>	1–25 μ M
THC, 11-OH-THC, 2-AG	Splenocytes <i>in vitro</i>	3–30 μ M
THC, CP 55,940, WIN 55,212-2	Lymphocytes <i>in vitro</i>	0.1–100 nM (0.0001–0.1 μ M)
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 μ M
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 μ M
THC	Peritoneal macrophages and monocytes	3–30 μ M
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 μ M 30 μ M
THC, CBD	Splenocytes and T cells <i>in vitro</i>	10 μ M
THC	Phorbol myristate acetate-differentiated macrophage <i>in vitro</i>	10–20 μ M
THC	Endotoxin-activated macrophages <i>in vitro</i>	10–30 μ M
THC	Peritoneal macrophages <i>in vitro</i>	10–30 μ M

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

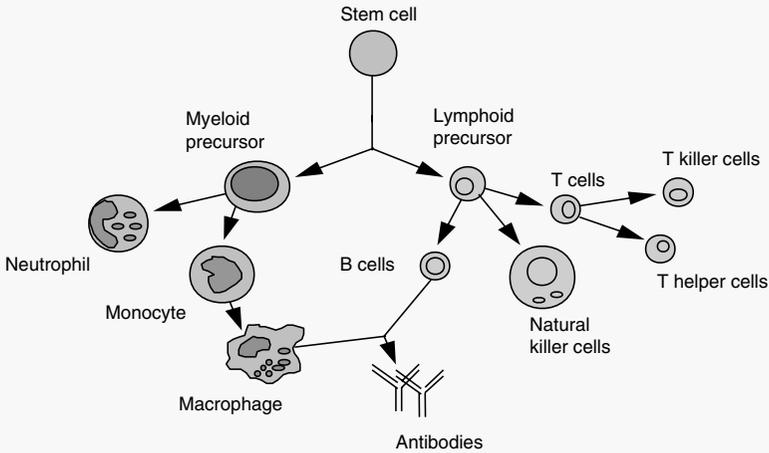
Box 2.1 Cells of the Immune System

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).

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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-

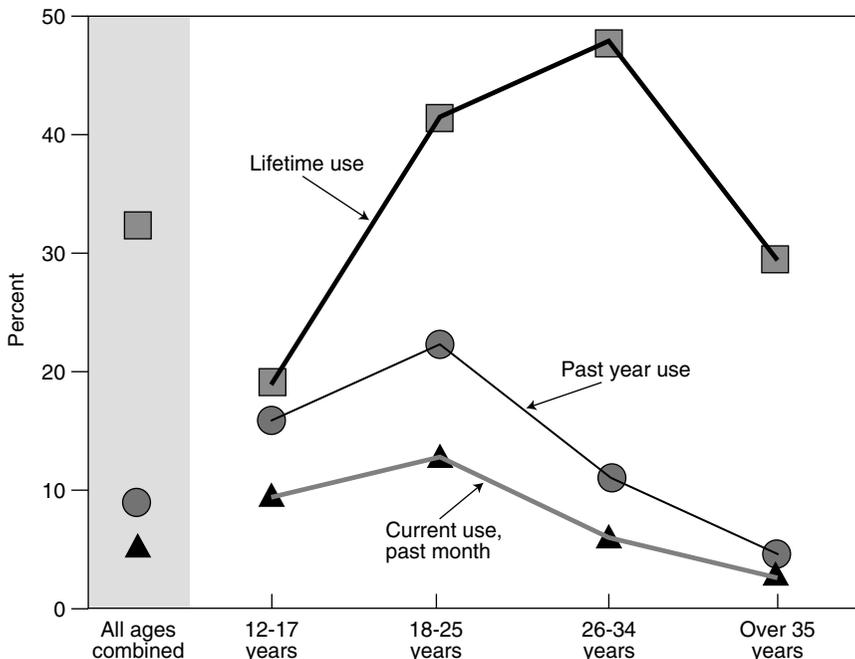


FIGURE 3.1 Age distribution of marijuana users among the general population.

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.

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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

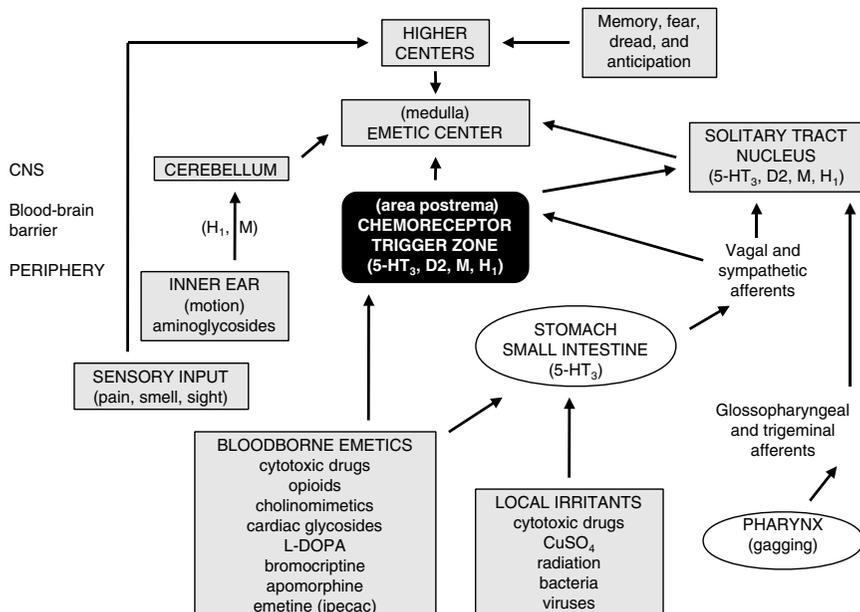


FIGURE 4.1 Emesis-stimulating pathways. SOURCE: Bruton, L.L. 1996. P. 929 in Hardman et al., eds., *The Pharmacological Basis of Therapeutics*, 9th edition. New York: McGraw-Hill. Reprinted with permission.

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.

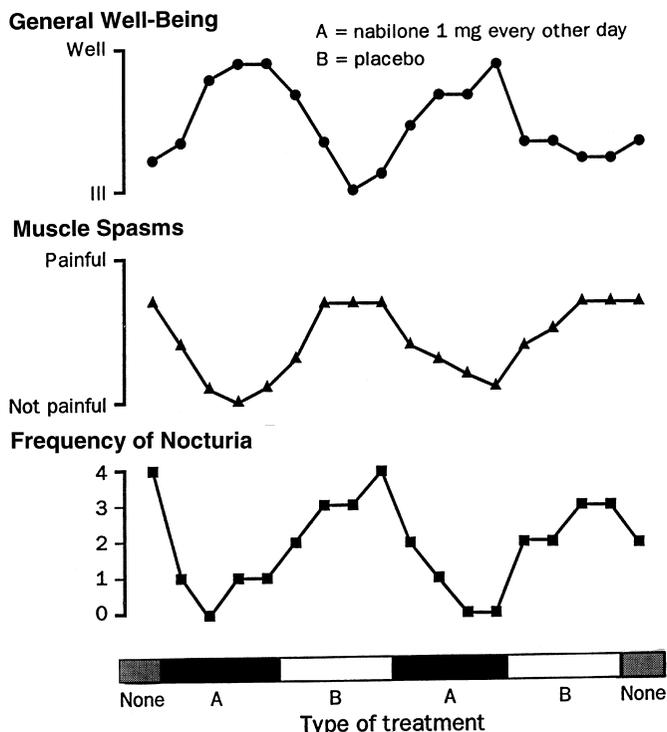


FIGURE 4.2 Effect of nabilone on multiple sclerosis symptoms. This figure shows the results of a trial in which a 45-year-old man with MS was given four-week treatments alternately with placebo and nabilone. The patient served as both experimental subject and control; his treatment sequence was nabilone-placebo-nabilone-placebo. 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 antitic 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}

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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

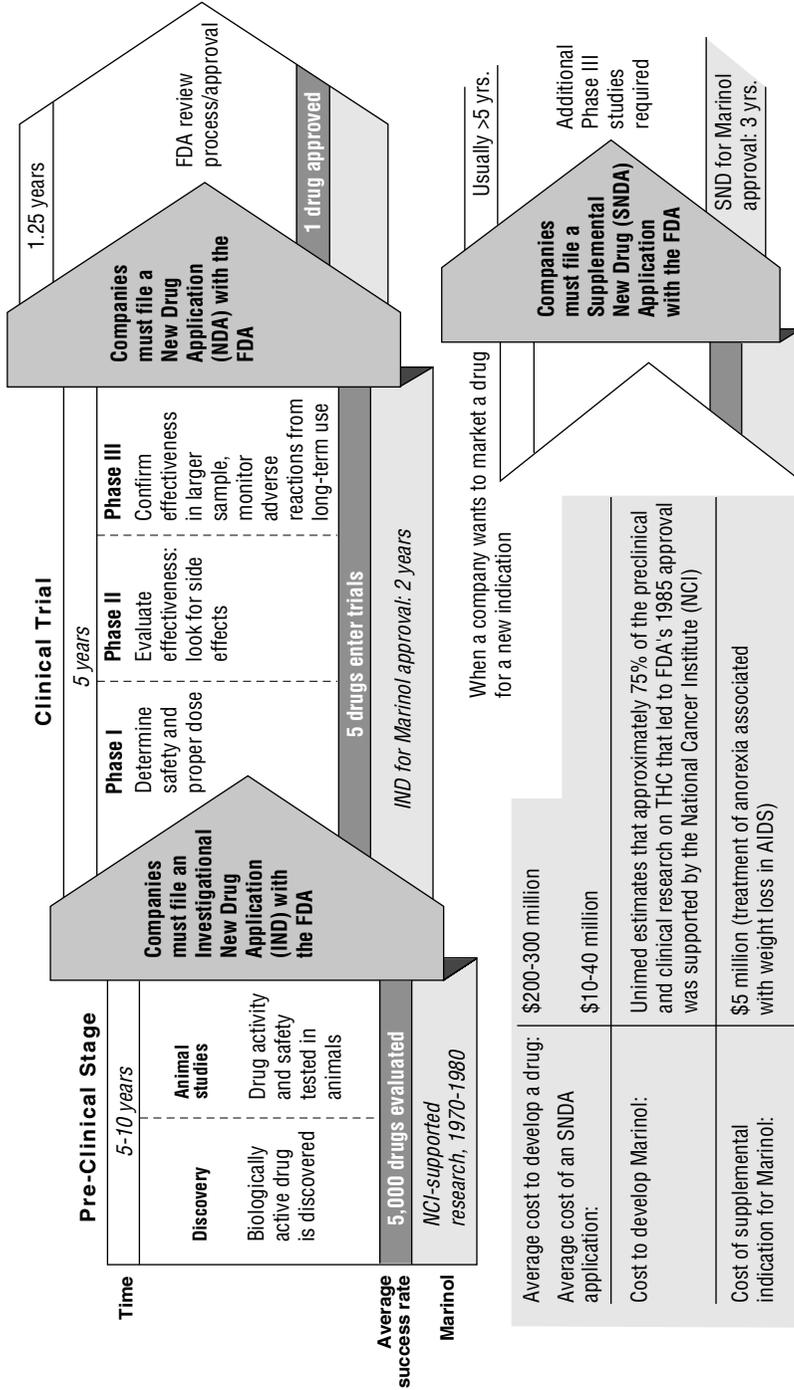


FIGURE 5.1 Stages of clinical testing.

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.

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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

Linda B. Ledger
O. J. Federation for Drug-Free
Communities

Bonnie Metcalf
Yuba County Compassionate Use
Co-Op

Carla Lowe

R. Mikin
American Academy of Addiction
Psychiatry

Ray Lozano
C.A.D.F.Y.

Alan D. Miller
The Rockefeller University

Patrick Magee
Orange County Hemp Council

Jim Montgomery

Robert L. Maginnis
Family Research Council

John P. Morgan
City University of New York
Medical School

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).

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SOURCES: LeCraw (1996) and 57 *Federal Register* 10499 (1992).

Index

A

- Addiction, *see* Craving; Dependence;
Tolerance; Withdrawal symptoms
- Adjunctive therapy, general, 4, 10, 145, 153,
157, 167, 172, 247
see also Pain, treatment of
- Administration of drugs, *see* Drug delivery
- Adolescents, 6, 15, 16, 90, 91, 96, 97, 98, 99,
101, 102, 104, 123, 126
- Affinity, receptors, 42, 44, 46, 51
defined, 42(footnote)
- African Americans, 173
- Age factors, 9, 16, 22, 92-93, 94, 95, 100, 117
adolescents, 6, 15, 16, 90, 91, 96, 97, 98,
99, 101, 102, 104, 123, 126
children, 96, 97, 101, 124-125, 139, 149,
167, 210
clinical trials, 139, 142
prenatal exposure, effects of, 124-125
see also Elderly persons
- Agonists, receptor, 34, 37, 38, 39, 43-47, 54,
56-57, 58, 64, 70
glaucoma, 176-177
listed, 44
market considerations, 209, 210, 212
neurological disorders, 166, 167, 168
see also SR 141716A; SR 144528
- AIDS, *viii*, 16, 18, 21, 22, 23, 107, 115-117,
120-121, 145, 178, 252
- AIDS wasting, 4, 8, 23, 154-158, 159, 177,
204-205, 207, 209, 234, 246, 248
clinical trials, 8, 156, 213, 245
defined, 154
individual patient account, 27-28
smoking of marijuana, 27-28, 156
- Alaska, *vii*, 17
- Alcohol use and abuse, 6, 88, 90, 92, 95, 96,
97, 100, 101, 117, 254
nausea and vomiting, 147
- Alternative medicine, general, 19, 20, 180,
215, 216, 217-218, 254-255
- Alzheimer's disease, 173, 204, 205, 209
- American Medical Association, 180, 244-
255 (*passim*)
- Amotivational syndrome, *see* Motivation
- Amphetamines, 21, 88, 240
- Analgesia, *see* Pain, treatment of
- Anandamide, 34, 41, 43-47, 48, 54, 194
- Animal studies, 3, 35, 36-81, 88, 89, 91, 111,
120, 122-123, 125, 140, 145, 195, 199,
212, 246
movement disorders, 164-165, 167, 170
relevance of, general, 36
- Anorexia, *see* Appetite; Wasting syndrome
- Anorexia nervosa, 159
- Antagonist, receptor, 34, 37, 39, 44, 55, 58, 70
market considerations, 205, 210, 211
nausea and vomiting, 151, 152-153
- Antiemesis, *see* Vomiting

Antigens, 59, 64, 66, 120
 Anxiety, 4, 10, 36, 84, 90, 109, 127, 142, 153, 165, 168, 203
see also Dysphoria; Euphoria; Sedation
 Appetite, *viii*, 3, 4, 10, 21, 23, 142, 144, 156-159 (passim), 173, 205, 209, 245, 248
see also Nausea; Vomiting; Wasting syndrome
 Arachidonic acid, 46, 47, 57
 Arachidonyl glycerol (2-AG), 43, 45, 46, 47, 64, 65
 Arizona, *vii*, 1, 17, 18, 104(footnote)
 Arthritis, 28-29
 Attitudes
 patients, 27-29, 153, 205-206
 physicians, prescribing marijuana, 152, 202
 risk perception, 104

B

Barbiturates, 143, 172
 Basal ganglia, 48-52, 164-166, 168
 B cells, 62, 64, 65, 66, 112
see also Lymphocytes, general
 Benzodiazepines, 3, 70, 161, 164, 168
 Blood pressure
 hypertension, 48, 84, 86, 90, 121, 158, 175
 hypotension, 121, 150, 151, 175
 Brain, general, 3, 35, 36-37, 48-49, 69, 70, 92, 170
 basal ganglia, 48-52, 164-166, 168
 cannabinoid receptors, 37-65, 69-70
 cerebellum, 46, 49, 50, 51, 53, 121, 122
 endogenous cannabinoid system, 43-51, 70
 globus pallidus, 49, 52, 53, 167
 hippocampus, 45-46, 49, 53
 putamen, 49, 52, 53, 166
 striatum, 46, 51, 53
 substantia nigra, 49, 51, 52, 53, 167, 168
 thalamus, 46, 49, 51, 52, 53, 55, 165, 167, 169
see Neurons, general
 British Medical Association, 180, 244-255 (passim)
 Bronchi, 113-114, 115, 119
 Buyers' clubs, *see* Cannabis buyers' clubs

C

Cachexia, 145, 154, 155, 158
see also AIDS wasting; Appetite; Wasting syndrome

Caffeine, 88
 California, *vii*, 1, 16, 17, 18, 101-102, 104, 204, 207
 Canada, 150
 Cancer
 smoking of marijuana as cause, 5, 114, 115, 117-121, 237
 treatment of, 22, 23, 142, 145, 154, 158, 159, 204-205; *see also* Chemotherapy
 Cannabidiol (CBD), 3, 36-37, 47, 60-61, 66, 122, 166, 171-172, 214
 Cannabinoids, general, *vii*, *viii-ix*, 2-4
 defined, 2, 25-26, 194
 defined substances, 4
 standards, general, 19, 213, 216, 217
see also THC
 Cannabinol, 25, 37, 64, 66, 110
see also THC
 Cannabis buyers' clubs, *viii*, 16, 20, 21, 22, 207
 defined, 20
 Cardiovascular system, 121-122, 251
see also Blood pressure
 Case studies, 15, 27-29, 117, 119-120, 254
 individual patient accounts, 27-29
 single-patient clinical trials, 139, 162
 CBD, *see* Cannabidiol
 Cellular biology, 5, 25, 35-59, 69-70, 118-119, 120-121
see also Genetics; Immune system; Receptors; Signal transduction
 Cerebellum, 46, 49, 50, 51, 53, 121, 122
 Cesamet, *see* Nabilone
 Chemotherapy, *viii*, 4, 16, 23, 144, 146-153 (passim), 177, 205, 207, 234, 245, 247, 248
 Children, 96, 97, 101, 124-125, 139, 149, 167, 210
see also Adolescents
 Chronic obstructive pulmonary disease, 114-115
 Clinical studies, 15, 30, 34-35, 137, 206, 233-234
 glaucoma, 177, 251
 movement disorders, 166, 169-170
 smoking of marijuana, 9-10
 Clinical trials, 7-8, 9-10, 34, 137, 141, 142-143, 203, 209, 211, 218
 age factors, 139, 142
 AIDS wasting, 8, 156, 213, 245
 animal studies *vs*, 36
 epilepsy, 170-172, 173
 Investigational New Drugs, 195, 196

movement disorders, 167, 168
 nausea and vomiting, 7-8, 142, 145-154,
 179, 245, 247
 pain, 7-8, 141-145, 179
 psychological effects, 5, 10, 109, 149
 recommendations, 4, 5, 7-8, 9-10, 178,
 179-180, 215, 245-255 (passim)
 regulatory requirements, 195, 196, 200,
 202, 208, 211, 213, 218, 256-257
 single-patient trials, 139, 162
 spasticity, 160-164, 165, 249
 standards for, 7-8, 10, 138-139, 179-180
 Cocaine, 3, 20, 70, 88, 90, 95, 102, 240
 Colorado, *vii*, 1
 Codeine, 143, 241
 Cognitive effects, 49, 83-84, 89, 105, 106-
 107, 108, 124-125
 disorientation, 4, 142, 203
 memory, 35, 49, 53, 56, 84, 89, 106, 144,
 173, 212
 see also Psychological effects
 Connecticut, 17
 Controlled Substance Act, 16-17, 102, 198-
 204 (passim), 210, 213-219 (passim)
 scheduling, 17, 102, 194, 198-213
 (passim), 216-217, 218, 240-241, 256-
 257
 Convulsions, *see* Seizures
 Cost factors, 9, 16, 206-207, 243
 antiemetics, 151, 152
 drug development, 195, 196, 203, 206,
 217-218
 CP 47,497, 210
 CP 55,244, 210
 CP 55,940, 44, 46, 56, 201
 Craving, 9, 90, 91-92
 CT-3, 67, 209
 Cytokines, 62, 66, 67, 112, 120, 157

D

DEA, *see* Drug Enforcement
 Administration
 Delivery modes, *see* Drug delivery
 Department of Health and Human
 Services, 199, 200, 201, 217
 see also National Institutes of Health
 Dependence, 6, 9, 57-59, 70, 84, 86, 237
 animal research, 35
 criteria, 87
 legal issues, 16
 marijuana as a gateway drug, 6-7, 9, 20-
 21, 98-101
 predictors of, 93-98, 99, 100, 101, 126
 see also Craving; Tolerance; Withdrawal
 symptoms
 Depression, 22, 23, 29, 84, 95, 105, 155, 159
 fluoxetine, 48
 see also Dysphoria
*Diagnostic and Statistical Manual of Mental
 Disorders*, 84, 87
 Diarrhea, 24, 155
 District of Columbia, 17
 Dizziness, 27, 121, 150, 158, 203
 Dopamine, 58, 88, 92, 167, 168
 Dosage factors, 137, 245, 248, 256
 affinity, 42(footnote)
 AIDS wasting, 156, 157, 158
 caffeine, 88
 cardiovascular effects, 121
 CBD, 36, 60-61
 cognitive effects, 107
 glaucoma treatment, 176, 177, 251
 immune system effects, 60-63, 64-67, 68
 morphine, 37
 multiple sclerosis treatment, 163
 neurological disorder treatment, 166, 169
 overdosing, 37, 109, 206
 pain treatment, 102, 142, 143, 149
 psychological effects, 84, 85, 105
 psychomotor effects, 51, 53, 85
 reproductive effects, 122, 125
 respiratory effects, 113
 THC, 88, 89, 91, 122, 142, 176, 203, 206,
 215, 255
 anxiety, 36, 142, 149
 glaucoma treatment, 176, 177, 251
 pain treatment, 102, 142, 143, 149
 psychoactive doses, 85
 vomiting, 147, 154
 vomiting, 147, 151, 152, 154
 see also Dependence; Tolerance
 Dronabinol, *see* Marinol
 Drug Awareness Warning System, 102-103
 Drug delivery, 7, 9, 151, 197, 199, 217, 239,
 242, 245
 inhalation, 7, 9, 57, 94, 150, 154, 165, 175,
 197, 203, 206, 215(footnote), 216,
 242, 247, 251, 255; *see* Smoking,
 marijuana
 injection, 39, 54, 57, 66, 67, 68, 85, 88, 94,
 100, 122, 150, 151, 152, 159, 174, 175,
 203

oral, 4, 9, 16, 57, 84, 89, 91, 121, 122, 142, 148-156 (*passim*), 163, 164, 165, 171, 174, 175, 202, 203, 205, 206, 207, 215, 242, 247, 249, 251
 suppositories, 206
 topical, 175, 176, 251
 Drug Enforcement Administration (DEA), 137, 198-202, 203-204, 208, 213, 214, 217
 Dysphoria, 5, 84, 126, 150, 159, 203
see also Anxiety; Depression
 Dystonia, 166, 168, 245, 250

E

Economic factors
 access and availability, general, 9, 194-198, 206-208, 213-214
 health insurance, 207
 malnutrition, 154, 155
 private investment, 178, 195-219
 public investment, 4, 137, 178, 211, 214, 218
see also Cost factors
 Efficacy, 9, 11, 14, 19, 20, 30, 54, 57, 88, 107, 108, 126, 144, 179, 217, 243, 256
 defined, 4-5
 regulatory requirements, 197, 212, 215
see also Clinical studies; Clinical trials
 Elderly persons, 21
 clinical trials, 139
 psychological effects, 4, 175
 Emesis, *see* Vomiting
 Emotional factors, *see* Psychological effects
 Endorphins (endogenous opioids), 35, 43
 Epidemiological Catchment Area Program, 97
 Epilepsy, 29, 170-173, 177, 245, 250-251
 Euphoria, 5, 16, 83-84, 85, 87, 88, 89, 92, 108, 144, 150, 203
 Eye diseases, *see* Glaucoma

F

Federal government, 194-202
see also Department of Health and Human Services; Drug Enforcement Administration; Food and Drug Administration; Legal issues and legislation; Public investment
 Fluoxetine, 48

Food and Drug Administration, 17, 20, 137, 138, 149, 156, 194-198, 199, 200, 202-203, 204, 205, 208, 209, 213, 215, 216, 217, 257
 Food and Drug Administration Modernization Act, 197(footnote)
 Food, Drug, and Cosmetic Act, 194, 213, 215, 256
 Foreign countries, *see* International perspectives; *specific countries*
 France, 69
 Funding, *see* Public investment

G

Gamma-aminobutyric acid (GABA), 50
 Gateway theory, 6-7, 9, 20-21, 98-101
 Gender factors, 20, 22, 94, 95, 115, 170-171
 Genetics, 5, 38, 42, 69, 118-119, 120
 dependence, 94, 97-98
 drug development, 19-20
 gene regulation, 37, 38
 reproductive system effects, 122-125
 transduction, 37, 38, 40-41, 43, 57; *see also* Agonists, receptor
see also Cellular biology; Receptor binding; Receptors
 Glaucoma, 9, 22, 24, 173-177, 234, 251-252
 agonists, receptor, 176-177
 dose effects, 176, 177, 251
 intraocular pressure, 175, 176, 251-252
 smoking of marijuana, 174, 175, 177, 251
 Globus pallidus, 49, 52, 53, 167

H

Hallucinations, 84, 90, 106
 Headaches, 151
see also Migraine headaches
 Health insurance, 207
 Heart, *see* Cardiovascular system
 Herbal medicine, general, *see* Alternative medicine, general
 Heroin, 88, 90, 92, 95, 99, 100, 240
 Hippocampus, 45-46, 49, 53
 Hispanics, 94-95
 Historical perspectives, 118
 antiemetics, 151
 legal issues, 16-18
 medicinal uses of marijuana, 16-19

research on marijuana, 33-34, 244-255
 HIV, *see* AIDS
 Hormones, 37, 48, 58-59, 66, 122, 123, 155, 157
 HortaPharm, 214-215, 218
 HU-210/HU-211, 44, 60, 64, 66, 67, 176, 201, 209, 211, 250
 Huntington's disease, 49, 166, 198
 Hyperalgesia, 54, 56, 141
 Hypertension, 48, 84, 86, 90, 121, 158, 175
 Hypotension, 121, 150, 151, 175

I

Immune system, 5, 37, 42, 51, 59-68, 70, 109-111, 112-113, 116-117, 120, 156, 158, 212, 233, 236, 245, 248, 252
 antigens, 59, 64, 66, 120
 cytokines, 62, 66, 67, 112, 120, 157
 dose effects, 60-63, 64-67, 68
 infections, 66-67, 112-113, 155, 236
 inflammatory/antiinflammatory effects, 67-68, 112-113, 142, 155, 209
 leukocytes, 59, 62, 64, 109-111, 120
 lymphocytes, general, 59, 62, 64, 112, 118, 155
 B cells, 62, 64, 65, 66, 112
 T cells, 59, 62, 64-65, 66, 112
 macrophages, 66, 112-113, 121
 multiple sclerosis, 160
see also AIDS
 Inactivation, 36, 46, 47, 48, 212
 Infections, 66-67, 112-113, 155, 236
see also AIDS; Receptors
 Inflammatory/antiinflammatory effects, 67-68, 112-113, 142, 155, 209
 Information dissemination, *see* Public information
 Insurance, *see* Health insurance
 International perspectives, 180, 244-255
 exporter of marijuana for research, 214-215, 218
 marijuana laws, 103-104
 seizure treatment, 171
 Single Convention on Narcotic Drugs, 217
see also specific countries
 Internet, *viii*, 16, 245
 Intraocular pressure, *see* Glaucoma
 Investigational New Drug applications (FDA), 195, 196, 198, 206, 213
 Israel, 209

L

Legal issues and legislation, 14, 16-18, 86, 126, 206-207, 215-216
 Controlled Substance Act, 16-17, 102, 198-204 (*passim*), 210, 213-219 (*passim*)
 scheduling, 17, 102, 194, 198-213 (*passim*), 216-217, 218, 240-241, 256-257
 Food and Drug Administration
 Modernization Act, 197(footnote)
 Food, Drug, and Cosmetic Act, 194, 213, 215, 256
 foreign/international, 103-104, 217
 Marijuana Tax Act, 16
 National Organization for the Reform of Marijuana Legislation, 17, 18, 200, 213
 Orphan Drug Act, 198, 205, 211
 patent law, 208-210
 Prescription Drug User Fee Act, 195
 referenda, *vii*, 1, 17, 18
 Single Convention on Narcotic Drugs, 217
 state legislation, 17, 18, 102-103, 200, 206-207
see also Regulatory issues
 Lethargy, *see* Motivation
 Leukocytes, 59, 62, 64, 109-111, 120
 Levonantradol, 44, 57, 142, 148, 149, 210
 Ligands, 37, 39, 40-41, 42, 45, 53, 64, 194
see also Agonists, receptor; Antagonist, receptor; Receptor binding
 Lipophilic substances, 25, 39, 175, 206
 Louisiana, 17
 LSD, 240
 Lungs, 5, 111-115, 117, 118, 119, 126, 236, 253
 Lymphocytes, general, 59, 64, 112, 118, 155
 B cells, 64, 65, 66, 112
 T cells, 59, 64-65, 66, 112

M

Macrophages, 66, 112-113, 121
 Malnutrition, *see* Appetite; Nutrition
 Marijuana, general
 active constituents, 36-37
 defined, 2, 24-25
 prevalence of use, 92-93, 137

- Marijuana and Health*, 2, 33
 Marijuana Tax Act, 16
 Marinol (dronabinol), 16, 44, 137, 149, 156, 158, 173, 194, 195, 240, 248
 development of, 193-194, 195, 197, 202-208, 210, 211, 216, 218
Medical Use of Cannabis, 244-245
 Memory, 35, 49, 53, 56, 84, 89, 106, 144, 212
 Alzheimer's disease, 173
 Men, *see* Gender factors
 Metabolic processes, 36-37, 65, 110, 203
 starvation, 154-155
 Methadone, 92, 240
 Methodology
 drug development, 19-20, 137, 193-219, 238-239, 255; *see also* Drug Enforcement Administration; Food and Drug Administration
 costs of, 195, 196, 203, 206, 217-218
 other research, 20-22, 24, 119-121, 162, 163, 213-214
 recommendations by non-committee organizations, 244-257
 psychological research, 104-105
 study at hand, 15-16, 225-243
 see also Case studies; Clinical studies; Clinical trials
 Migraine headaches, 22, 23, 143-144, 209, 213
 Minority groups, *see* Racial/ethnic factors
 Mood effects, 21, 69, 84, 89, 92, 99, 105, 108, 143, 144, 153, 154, 161, 165, 248
 see also Anxiety; Depression; Dysphoria; Euphoria; Sedation
 Morphine, 37, 41, 55, 240
 Motivation, 58, 105, 107-108, 158, 168, 237, 254
 Motor effects, *see* Movement disorders; Psychomotor effects
 Movement disorders, 4, 160, 165-170, 177, 233, 245, 249-250
 animal studies, 164-165, 167, 170
 Parkinson's disease, 49, 167, 168, 198, 209
 seizures, 22, 29, 90, 170-173, 177, 245, 250-251
 Tourette's syndrome, 167-168
 see also Basal ganglia; Psychomotor performance; Spasticity
 Mucositis, 144
 Multiple sclerosis, 9, 22, 23, 143, 160-161, 162, 163, 170, 198, 209, 245
 individual patient account, 28
 Muscle spasticity, *see* Spasticity
- N**
- Nabilone, 44, 148, 149, 161, 162, 163, 174, 202, 246, 248, 249
 Naloxone, 37, 92
 National Cancer Institute, 202
 National Household Survey on Drug Abuse, 104
 National Institute of Drug Abuse, 213-214
 National Institutes of Health, 178, 180, 194-195, 202, 213-214, 215, 244-255
 (*passim*)
 National Organization for the Reform of Marijuana Legislation, 17, 18, 200, 213
 Nausea
 antagonist, receptors 151, 152-153
 clinical trials, 7-8, 142, 145-154, 245, 247
 opioids, 140
 palliation, 3, 4, 7-8, 9, 10, 16, 21, 23, 27, 29, 142, 144, 145-154, 159, 164, 202, 205, 207, 234, 245, 247, 248
 withdrawal symptoms, 6, 90, 127
 see also Appetite; Vomiting
 Netherlands, 103-104, 180, 214, 244, 245, 246, 249-255 (*passim*)
 Neurology and neurological disorders, 233, 234, 242, 245, 246, 251
 Alzheimer's disease, 173, 204
 dizziness, 27, 121, 150, 158, 203
 glaucoma, 173-176 (*passim*)
 seizures, 22, 29, 90, 170-173, 177, 245, 250-251
 see Brain; Movement disorders; Multiple sclerosis; Spasticity; Spinal cord
 Neurons, general, 2, 37, 38, 46, 47, 48, 49-50, 53, 55, 167, 211
 Neuroprotection, 47, 67, 70, 176, 209, 211
 Neurotransmitters, 37, 38, 43, 48, 50, 53, 54, 88, 147, 168, 211
 dopamine, 58, 88, 92, 167, 168
 see also Endorphins; Gamma-aminobutyric acid; Serotonin
 Nevada, *vii*, 1, 17
 New drug applications (FDA), 195-197, 203, 215, 257
 New Hampshire, 17
 Nicotine, 3, 70, 88, 90, 92, 96, 97, 100
 see also Tobacco
 Norway, 104
 Nutrition, 154-156, 158
 anorexia nervosa, 159
 see also Appetite; Wasting syndrome

O

- Office of National Drug Control Policy, *vii*, 1
- Ohio, 17
- Older persons, *see* Elderly persons
- Opioids, 3, 35, 37, 43, 53, 54, 55, 58, 69, 70, 88, 92, 102, 233, 246
 - heroin, 88, 90, 92, 95, 99, 100, 240
 - morphine, 37, 41, 55, 240
 - pain treatment, 140, 142
- Oregon, *vii*, 1, 17
- Orphan Drug Act, 198, 205, 211

P

- Pain, treatment of, *viii*, 3, 4, 7, 9, 10, 11, 20-22, 23, 24, 28-29, 84, 159, 164, 210, 233, 234, 241, 245-247
 - clinical trials, 7-8, 141-145, 179
 - dose effects, 102, 142, 143, 149
 - hyperalgesia, 54, 56, 141
 - market for, 210, 212
 - neurophysiology of, 35, 53-56, 70
 - sedation, 5, 10, 109, 127, 140, 144, 145, 150, 161, 164, 168, 241
 - standards of analgesic usefulness, general, 140-141
 - usefulness of analgesics, general, 140-141
- Pain, types of, 141-145, 166
 - acute, 54, 67-68, 141-142
 - chronic, 8, 21, 22, 23, 30, 53, 54, 67-68, 138, 142-143
 - definitional issues, 139-140, 141
 - depression, 22, 23, 29, 48, 84, 95, 105, 155, 159
 - dysphoria, 5, 84, 126, 150, 159, 203
 - inflammatory/antiinflammatory effects, 67-68, 112-113, 142, 155, 209
 - surgical, 142, 145, 247
 - withdrawal, 3, 6, 35, 58-59, 70, 84, 86, 87, 89-91, 127, 143-144
- Paranoia, 84, 105
- Parkinson's disease, 49, 167, 168, 198, 209
 - see also* Substantia nigra
- Peer review, 9, 15
- Performance, *see* Psychomotor performance
- Pharmaceutical companies, *see* Private sector
- Political and social factors, *vii*, 1, 2, 6-7, 13-15, 17-19, 92, 93, 94, 98, 99, 202, 234
 - National Organization for the Reform of Marijuana Legislation, 17, 18, 200, 213
 - see also* Legal issues and legislation; Referenda
 - Polycyclic aromatic hydrocarbons, 117, 119
 - Potency, 41, 46, 214-215
 - Pregnancy, 122-125, 126, 139, 145
 - Prescription Drug User Fee Act, 195
 - Private sector, 178, 195-219
 - Prostaglandins, 44, 46, 176
 - Prozac, *see* Fluoxetine
 - Psychiatric disorders, *see* Schizophrenia
 - Psychological effects, 3, 4-5, 44, 54, 65, 83-92, 101, 104-109, 126, 233, 237, 253-254
 - anorexia nervosa, 159
 - anxiety, 4, 10, 36, 84, 90, 109, 127, 142, 153, 165, 168, 203
 - clinical trials, 5, 10, 109, 149
 - dependence predictors, 95-96, 99, 100, 101, 126
 - depression, 22, 23, 29, 48, 84, 95, 105, 155, 159
 - dose effects, 84, 85, 105
 - DSM-IV, 84, 87
 - dysphoria, 5, 84, 126, 150, 159, 203
 - elderly patients, 4, 175
 - euphoria, 5, 16, 83-84, 88, 92, 108, 150, 203
 - hallucinations, 84, 90, 106
 - mood disorders, general, 23, 24
 - motivation, 58, 105, 107-108, 158, 168, 237, 254
 - paranoia, 84, 105
 - receptor physiology, 35
 - schizophrenia, 105, 106, 159, 253
 - seizures, impacts of, 172
 - smoking of marijuana, 5-6, 10-11, 104-109
 - withdrawal, 3, 6, 35, 58-59, 70, 84, 86, 87, 89-91, 127, 143-144
 - see also* Cognitive effects
 - Psychomotor performance, 5, 85, 89, 107, 108, 125-126, 254
 - dizziness, 27, 121, 150, 158, 203
 - dose effects, 51, 53, 85
 - movement disorders
 - physiology of, 35, 49, 51-53, 55
 - see also* Spasticity
 - Public information, *viii*, 101
 - Internet, *viii*, 16, 245
 - Public investment, 4, 137, 178, 211, 214, 218
 - Putamen, 49, 52, 53, 166

R

- Racial/ethnic factors, 94-95, 173
- Receptor binding, 37, 39-45, 64, 194, 211
 affinity, 42, 44, 46, 51
 ligands, 37, 39, 40-41, 42, 45, 53, 64, 194
 potency, 41, 46
see also Agonists, receptor; Antagonist, receptor
- Receptors, 2, 3, 33, 34, 35, 37-65, 69-71, 86, 110, 144, 159, 169, 172, 176-177
 anandamide, 34, 41, 43-47, 48, 54, 194
 brain, 41, 49, 51-59
 immune system, 59-64
 nausea and vomiting, 146, 147, 152, 153
 serotonin, 48, 151, 152-153, 159, 205
- Referenda, *vii*, 1, 17, 18
- Regulatory issues, 14, 211, 213-218
 clinical trials, 195, 196, 200, 202, 208, 211, 213, 218, 256-257
 THC, 200-208, 214-215
see also Drug Enforcement Administration; Food and Drug Administration; Legal issues and legislation; Standards
- Reproductive system effects, 122-125, 126, 139, 145, 253
- Research methodology, *see* Methodology
- Respiratory system, 5-6, 10, 88, 113-115, 119-120, 127, 146, 236, 253
see also Lungs

S

- Scheduling, 17, 102, 194, 198-213 (*passim*), 216-217, 218, 240-241, 256-257
- Schizophrenia, 105, 106, 159, 253
- Sedation, 5, 10, 109, 127, 140, 144, 145, 150, 161, 164, 168, 241
- Seizures, 22, 29, 90, 170-173, 177, 245, 250-251
 types of, 170
- Serotonin, 48, 151, 152-153, 159, 205
- Side effects, general, 9, 27, 28, 127, 138, 140, 151, 203, 243, 246
 marijuana use, 34, 145, 150, 152, 158, 161, 170, 172, 173, 177
see also Anxiety; Chemotherapy; Memory; Nausea; Sedation; Vomiting
- Signal transduction, 37, 38, 40-41, 43, 57
see also Agonists, receptor; Cellular biology

- Single Convention on Narcotic Drugs, 217
- Sleep, 6, 27, 37, 49, 83, 90, 127, 160, 164, 165
- Smoking, marijuana, 2, 4, 5, 7-8, 47, 83, 85, 91, 104, 111-127, 177-178, 216, 254-255
 AIDS wasting, 27-28, 156
 carcinogenic effects, 5, 114, 115, 117-121, 237
 defined, 2
 glaucoma, 174, 175, 177, 251
 individual patient accounts, 27-29
 movement disorders, 167
 physiological effects, 5-6, 10-11, 104-109
 spasticity, 161, 163
 tolerance, 57, 89
 vomiting, control of, 150, 152, 153, 154, 179, 247
 wasting syndrome, 27-28, 156, 159
- Smoking, tobacco, *see* Tobacco
- Social factors, *see* Political and social factors
- Spasticity, 23, 24, 143, 169, 245, 249
 clinical trials, THC, 160-164, 165, 249
 multiple sclerosis, 9, 22, 23, 28, 143, 160-161, 162, 163, 198
 smoking of marijuana, 161, 163
- Spinal cord, 49, 54, 55-56,
 injury, 23, 145, 159-160, 161, 163-164, 198, 245, 249
- Spleen, 46, 59, 64, 66
 SR 141716A, 34, 44, 57-58, 65, 69
 SR 144528, 34, 44
- Standards
 analgesic usefulness, general, 140-141
 cannabinoid drugs, 19, 213, 216, 217
 clinical trials, 7-8, 10, 138-139, 179-180
 DSM-IV, 84, 87
- State-level action
 legislation, 17, 18, 102-103, 200, 206-207
 referenda, *vii*, 1, 17, 18
see also specific states
- Striatum, 46, 51, 53
- Substantia nigra, 49, 51, 52, 53, 167, 168

T

- Tardive dyskinesia, 166, 168
- Taxes, 16
- T cells, 59, 62, 64-65, 66, 112, 120
see also Lymphocytes, general
- Tetrahydrocannabinol, *see* Marinol; THC
- Thalamus, 46, 49, 51, 52, 53, 55, 165, 167, 169

THC, *viii*, 2, 3, 4, 5, 10, 25, 26, 36-37, 39, 41, 71, 85, 88, 107, 109, 127, 177, 212, 234, 246, 247, 255
 analogues, 44
 Alzheimer's disease, 173
 cardiovascular system, 121-122
 dependence, 57-59
 dose effects, 88, 89, 91, 122, 142, 176, 203, 206, 215, 255
 anxiety, 36, 142, 149
 glaucoma treatment, 176, 177, 251
 pain treatment, 102, 142, 143, 149
 psychoactive doses, 85
 vomiting, 147, 154
 endogenous cannabinoids and, 43-48
 epilepsy, 170
 glaucoma, 174-175, 176-177, 251-252
 immune system, 59-68 (*passim*), 110, 117
 levonantradol, 44, 57, 142, 148, 149, 210
 Marinol (dronabinol), 16, 44, 137, 149, 156, 158, 173, 194, 195, 240, 248
 development of, 193-194, 195, 197, 202-208, 210, 211, 216, 218
 pain treatment, 7-8, 102, 141-145, 149, 179
 regulatory issues, 200-208, 214-215
 reproductive system effects, 122-125
 spasticity, clinical trials, 160-164, 165, 249
 tolerance, 56-57, 89, 121
 vomiting, clinical trials, 148-150, 153
 Tobacco, *viii*, 5, 6, 95, 96, 97, 111-112, 113-114, 117, 118-119, 123
 see also Nicotine
 Tolerance, 3, 56-57, 70, 84, 86, 88-89, 121, 126-127, 233, 237
 analgesics, usefulness of, 140
 defined, 86, 87
 smoking of marijuana, 57, 89
 THC, 56-57, 89, 121
 see also Dependence
 Tourette's syndrome, 167-168
 2-AG, *see* Arachidonyl glycerol

U

Unimed Pharmaceuticals, Inc., 202-205
 United Kingdom, 180, 209, 211, 218, 244-255 (*passim*)

V

Vermont, 17
 Virginia, 17
 Vomiting, 3, 4, 10, 21, 23, 27, 29, 202, 205, 207, 210, 234, 248
 antagonists, receptors, 151, 152-153
 clinical trials, 7-8, 142, 145-154, 179, 245, 247
 cost of antiemetics, 151, 152
 dose effects, 147, 151, 152, 154
 drug delivery route, 148-154 (*passim*), 179, 247
 smoking of marijuana, 150, 152, 153, 154, 179, 247
 THC, 148-150, 153
see also Nausea

W

Washington, D.C., *see* District of Columbia
 Washington State, *vii*, 1, 17
 Wasting syndrome, 9, 23, 24, 28-29, 144, 154-159, 234, 248
 Alzheimer's disease, 173
 definitions, 153-154
 smoking of marijuana, 27-28, 156, 159
 see also AIDS wasting; Appetite
 WIN 55,212, 42, 44, 64, 65, 88
 Wisconsin, 17
 Withdrawal symptoms, 3, 6, 35, 58-59, 70, 84, 86, 89-91, 127, 143-144
 defined, 86, 87
 Women, *see* Pregnancy; Reproductive system effects
 World Health Organization, 244-255 (*passim*)
 World Wide Web, *see* Internet

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

As requested by Minnesota Statute 3.197: This report cost approximately \$58,500 to prepare, including staff time, printing and mailing expenses.

Upon request, this material will be made available in an alternative format such as large print, Braille or audio recording. Printed on recycled paper.

Table of Contents

Minnesota Medical Cannabis Program: Patient Experiences from the First Program Year.....	1
Executive Summary	9
Participation	9
Medical Cannabis Purchasing Patterns	10
Medical Cannabis Use Patterns.....	10
Benefits.....	11
Adverse Side Effects	13
Affordability and Suggestions for Improving the Program	13
1. Introduction	14
2. Patients and Caregivers Registered in the First Program Year	16
Qualifying Condition	16
Age and Gender	18
Age by Qualifying Condition	19
Race and Ethnicity	21
Registered Caregivers and Parents/Legal Guardians	21
Geographic Distribution and Distance to Nearest Cannabis Patient Center	23
From Certification to Program Approval: How Long Does it Take for Patients?	27
Time from Certification to Program Approval	28
Time from Certification to Annual Enrollment Fee Payment	28
Time from Annual Enrollment Fee Payment and Program Approval	28

From Certification to Program Approval: Conclusions	28
Re-Enrollment.....	29
3. Health Care Practitioners Registered in the First Program Year	31
Healthcare Practitioner Count, Age and Gender	31
Registered Physician Specialties and Licensures.....	35
Advanced Practice Registered Nurse Licensures	37
Summary.....	37
4. Frequency and Duration of Medical Cannabis Purchases	38
Time from Program Approval to First Medical Cannabis Purchase	38
Time Between Purchases	39
Purchasing Activity in First Four Months of Program Participation.....	40
Patients Who Stopped Purchasing Medical Cannabis.....	41
Frequency and Duration of Medical Cannabis Purchases: Conclusions	43
5. Medical Cannabis Use Patterns	44
Most Frequently Purchased Product(s).....	47
Severe and Persistent Muscle Spasm Patients	51
Cancer Patients.....	55
Seizure Patients.....	58
Crohn’s Disease Patients	60
Terminal Illness Patients	62
HIV/AIDS Patients.....	64
Tourette Syndrome Patients	66
Glaucoma Patients	68

ALS Patients	70
Medical Cannabis Use Patterns: Conclusions.....	72
6. Benefits	73
Summary.....	73
Benefits Reported on Surveys	78
Survey Methodology and Data Preparation	78
Patient Experience Survey Results	79
Patient Experience Survey Response Rate.....	79
Patient Perceptions of Benefits from Medical Cannabis	81
All Qualifying Conditions.....	81
Severe and Persistent Muscle Spasms.....	82
Cancer	83
Seizures	84
Crohn’s Disease	85
Terminal Illness	86
HIV/AIDS.....	87
Tourette Syndrome	88
Glaucoma	89
ALS.....	90
Patient Perceptions of Types of Benefits from Medical Cannabis Treatment.....	90
Symptom Improvement from Medical Cannabis Treatment.....	91
Patient Perceptions of Global Health Benefits from Medical Cannabis	94
Health Care Practitioner Survey Results.....	98

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST PROGRAM YEAR

HCP Survey Response Rate.....	98
Healthcare Practitioner Perceptions of Benefit	100
All Qualifying Conditions.....	101
Severe and Persistent Muscle Spasms.....	102
Cancer	103
Seizures	104
Crohn’s Disease	105
Terminal Illness	106
HIV/AIDS.....	107
Tourette Syndrome	108
Glaucoma	109
ALS.....	110
HCP Perceptions of Symptom Improvement from Medical Cannabis Treatment	111
HCP Perceptions of Global Health Benefits from Medical Cannabis Treatment	115
Additional Clinical Observations.....	118
Patient Versus HCP Perceptions of Benefit from Medical Cannabis.....	119
Severe and Persistent Muscle Spasms	120
Cancer.....	121
Seizures.....	122
Crohn’s Disease	123
Terminal Illness.....	123
HIV/AIDS	124
Tourette Syndrome	125

Glaucoma.....	126
ALS.....	127
Benefits Reported on Surveys: Conclusions.....	127
Benefits Reported on the Patient Self-Evaluation.....	128
Standard 8 Symptom Measures.....	128
Overall Results on Standard 8 Symptom Measures.....	131
Results on Standard 8 Symptom Measures Stratified by Qualifying Condition ...	134
Condition-Specific Symptom Measures.....	139
Severe and Persistent Muscle Spasms.....	142
Cancer: Nausea and Vomiting.....	144
Cancer: Cachexia and Severe Wasting.....	144
Seizures.....	144
Crohn’s Disease.....	147
Terminal Illness.....	148
HIV/AIDS.....	148
Tourette Syndrome.....	148
Glaucoma.....	149
ALS.....	151
Benefits Reported on the Patient Self-Evaluation: Conclusions.....	152
7. Adverse Side Effects.....	153
Summary.....	153
Adverse Side Effects Reported on the Patient Self-Evaluation.....	154
Severe Adverse Side Effects.....	158

PSE-Reported Adverse Side Effects: Conclusions.....	161
Adverse Side Effects Reported on Surveys.....	165
Patient-Reported Negative Effects of Medical Cannabis.....	165
HCP-Reported Negative Effects from Medical Cannabis	166
Adverse Side Effects Reported on Surveys: Conclusions	167
Adverse Event Reporting to Manufacturers.....	168
8. Affordability and Suggestions for Improving the Program.....	169
Patient Perceptions of Affordability.....	169
Patient Perceptions of Online Registry	170
Patient Perceptions of Office of Medical Cannabis Call Center	171
Patient Perceptions of Office of Medical Cannabis Website	172
Patient Suggestions	172
Suggestions and Information Requests from Healthcare Practitioners.....	173
Appendix A: Patient-Reported Benefits from Surveys	34 pages
Appendix B: Healthcare Practitioner-Reported Benefits from Surveys	8 pages
Appendix C: Healthcare Practitioner-Reported Clinical Observations from Surveys	5 pages
Appendix D: Symptom Results from the Patient Self-Evaluation	287 pages
Appendix E: Patient-Reported Negative Effects from Surveys	16 pages
Appendix F: Healthcare Provider-Reported Negative Effects from Surveys	4 pages
Appendix G: Patient Suggestions for Improving the Program from Surveys	36 pages
Appendix H: Healthcare Practitioner Suggestions for Improving the Program and Requests for Additional Information from Surveys	7 pages

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

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST
PROGRAM YEAR

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.

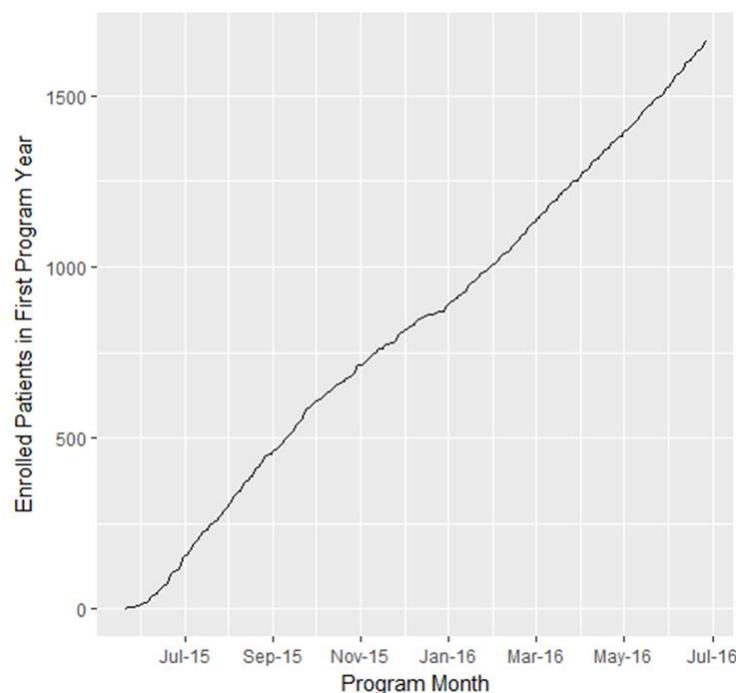
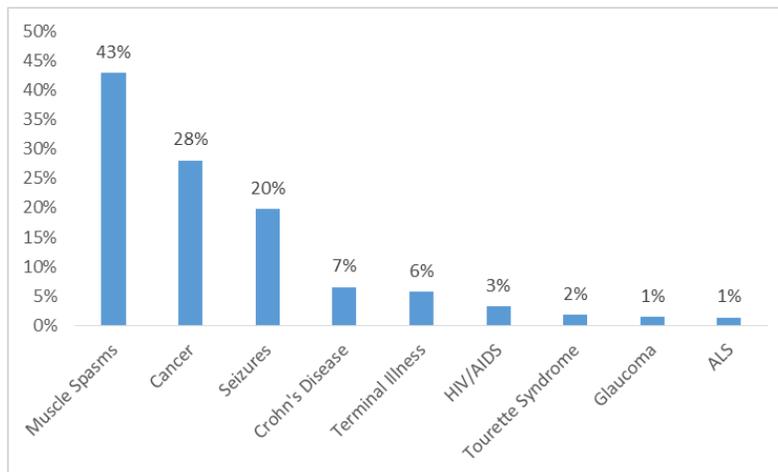


Table 2.1. Patient counts by qualifying condition.

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

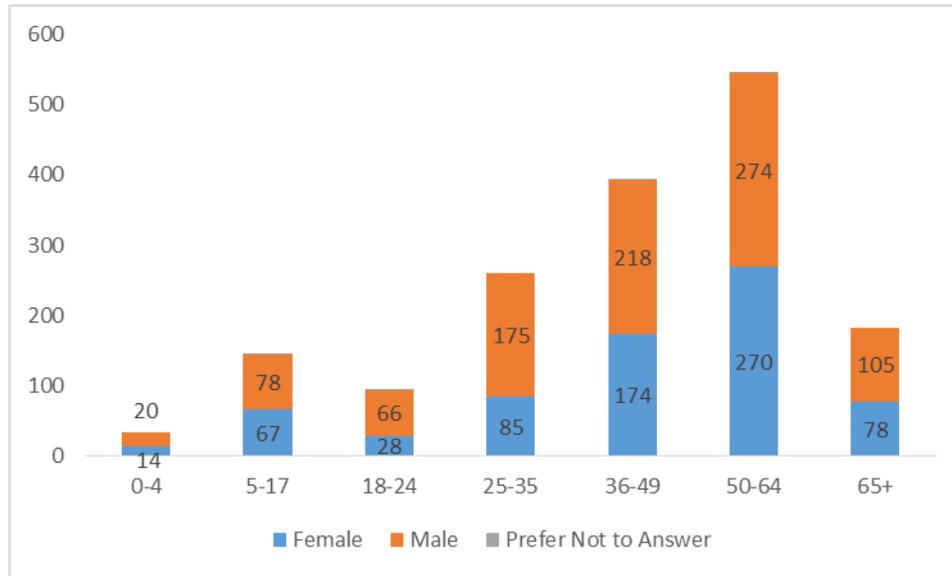
At the time of certifying that a patient has a medical condition qualifying them for the medical cannabis program, the certifying healthcare practitioner enters the patient’s date of birth. Additionally, during registration, patients are asked to report gender and race/ethnicity but are not required 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

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST PROGRAM YEAR

	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>

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST
PROGRAM YEAR

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.

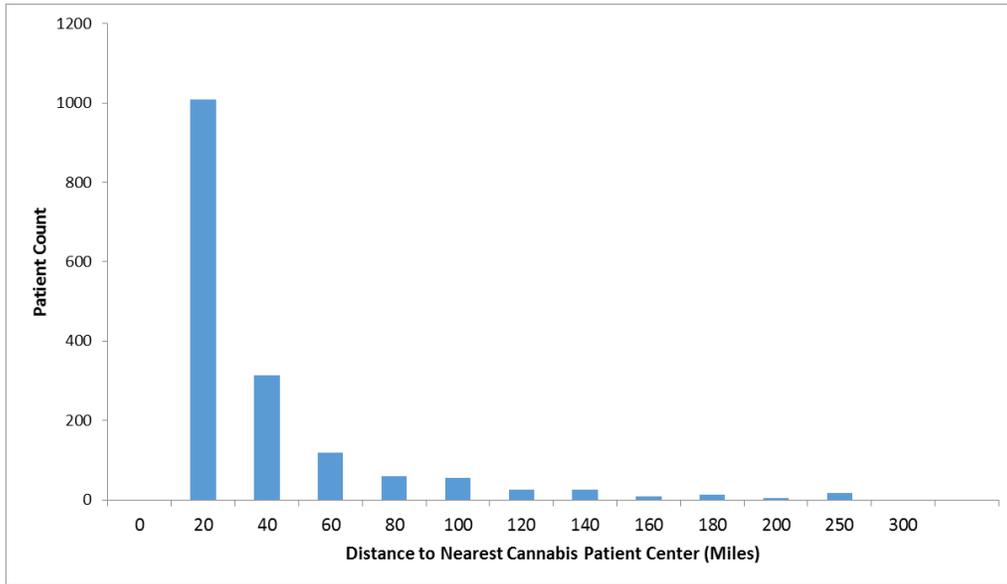
Table 2.7. Geographic distribution of patients by ZIP code prefix.

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.

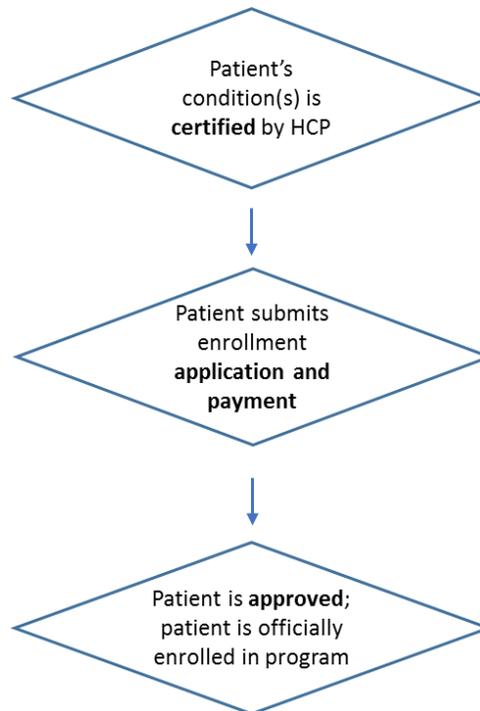
Figure 2.4. Distribution of one-way distance from patient home to nearest cannabis patient center.



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.

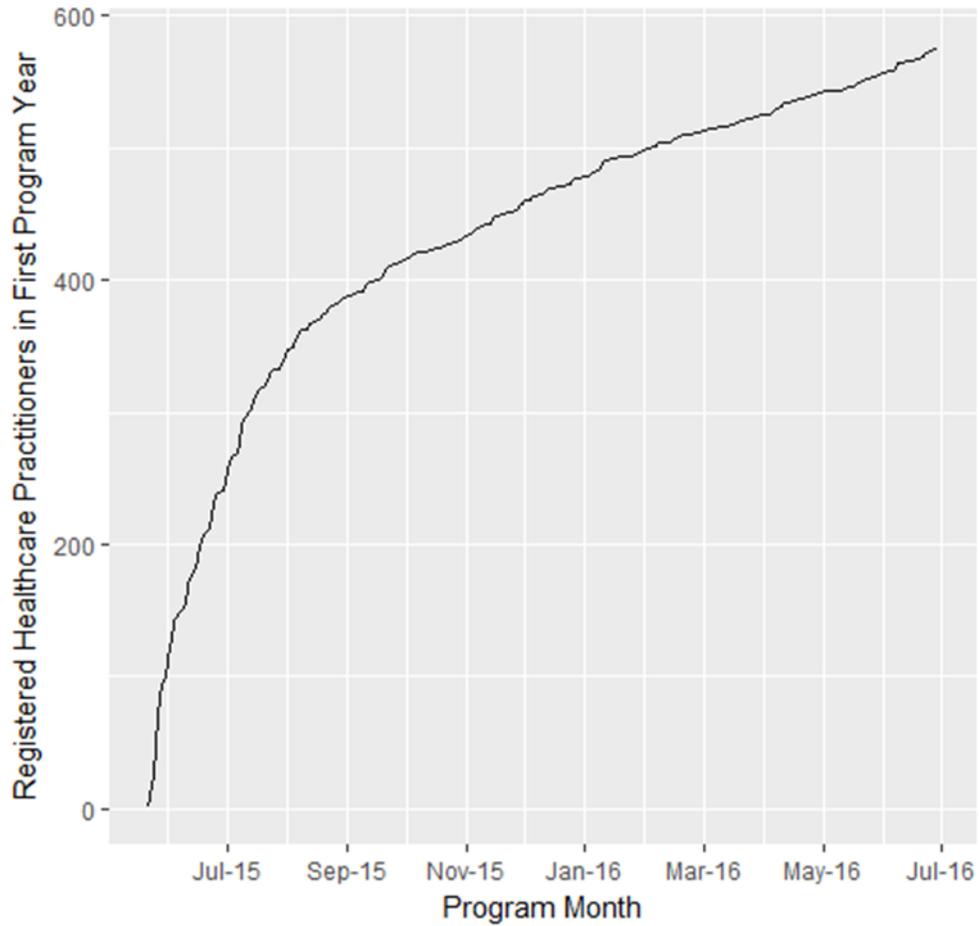


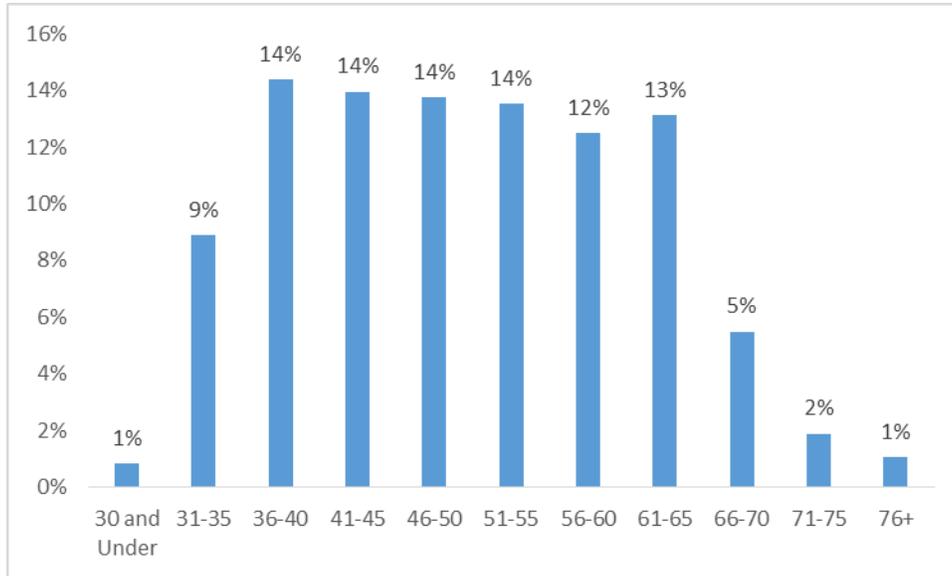
Table 3.1. Healthcare practitioner by type, with gender and average age.

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.

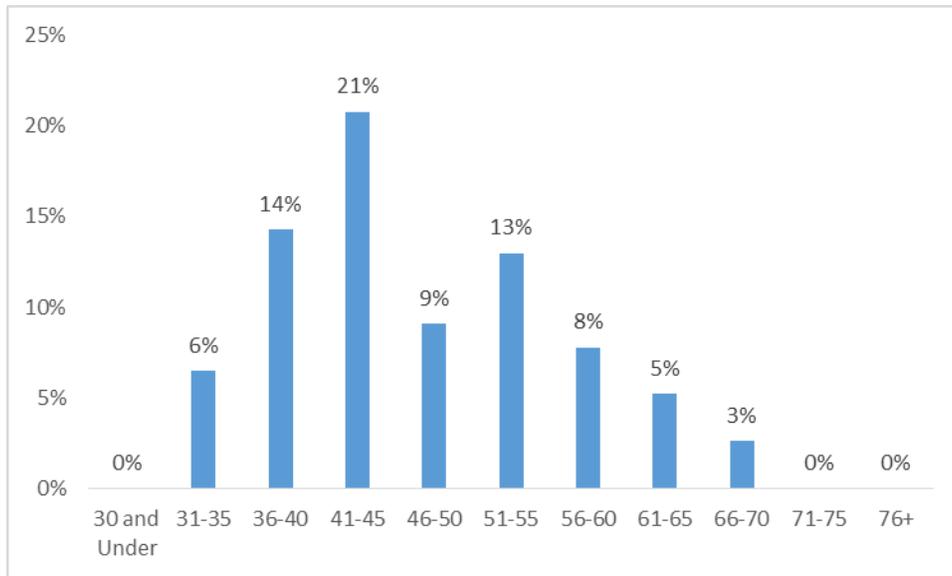
More detailed representations of age distribution among registered physicians, PAs and APRNs are available in Figures 3.2-3.4. Figure 3.2 shows the age distribution in 5 year increments of physicians enrolled in the first program year; most physicians fall between ages 36-65 years (81%) with relatively 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).



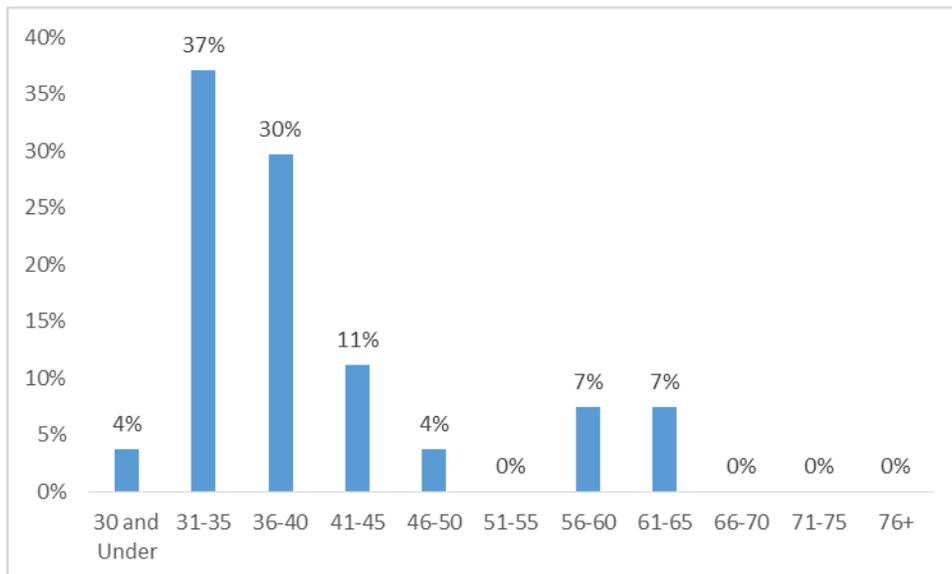
Note: Age data was not publicly available for three physicians registered in the first program year.

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

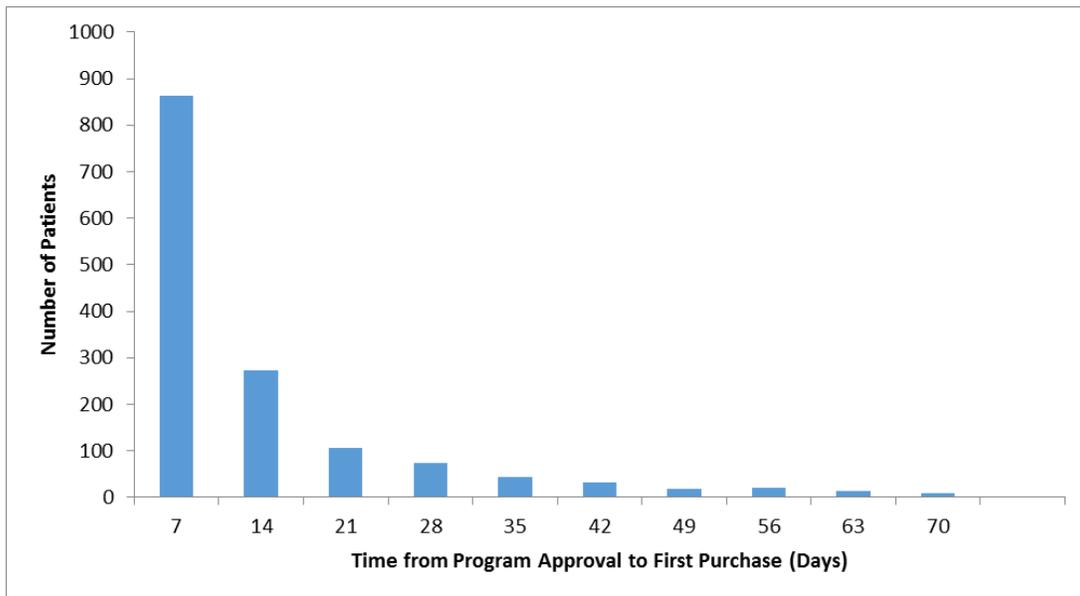
In the first year of the Minnesota Medical Cannabis program, 577 licensed healthcare practitioners registered as certifying providers with the program, predominantly physicians (82%). There were age and gender differences across the HCP types; physicians tended to be older and male; PAs and APRNs tended 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.

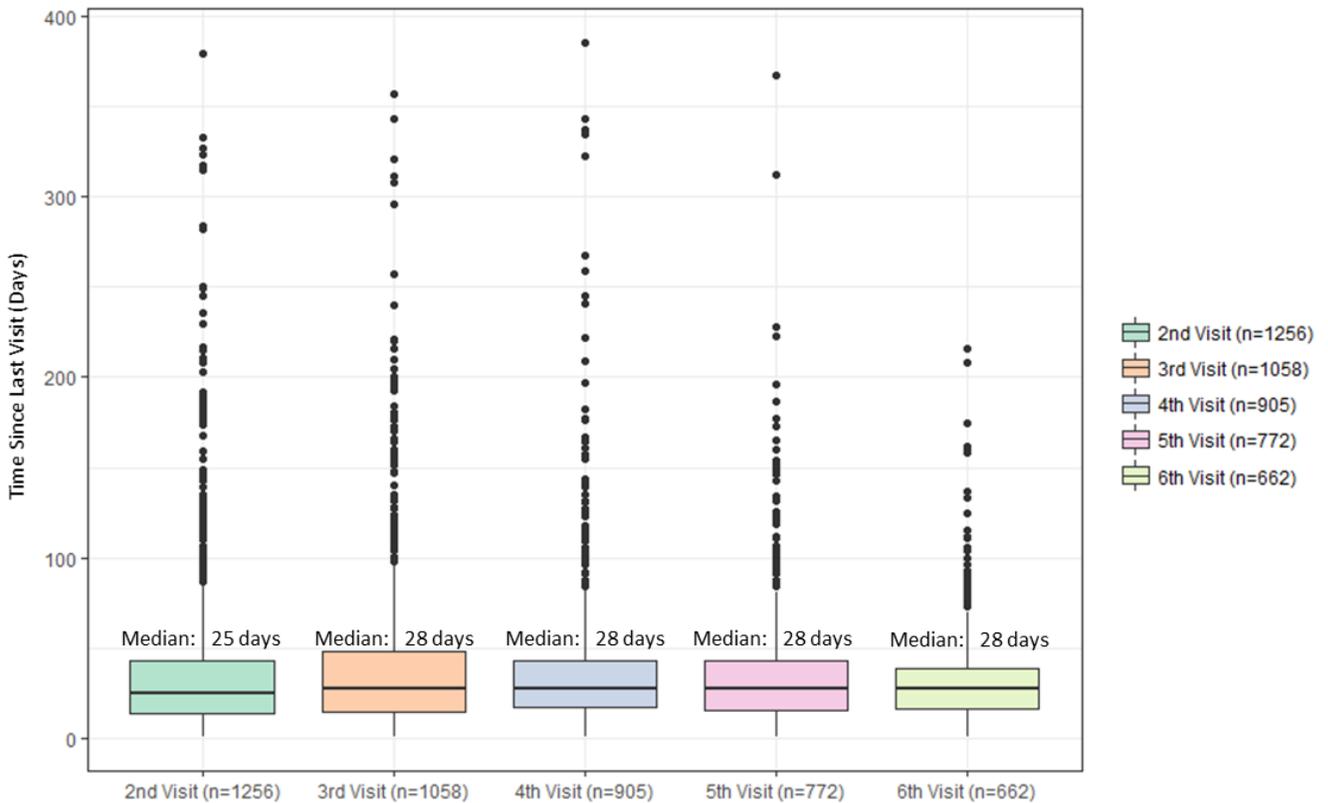
Figure 4.1. Time from patient approval to first medical cannabis purchase.



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.



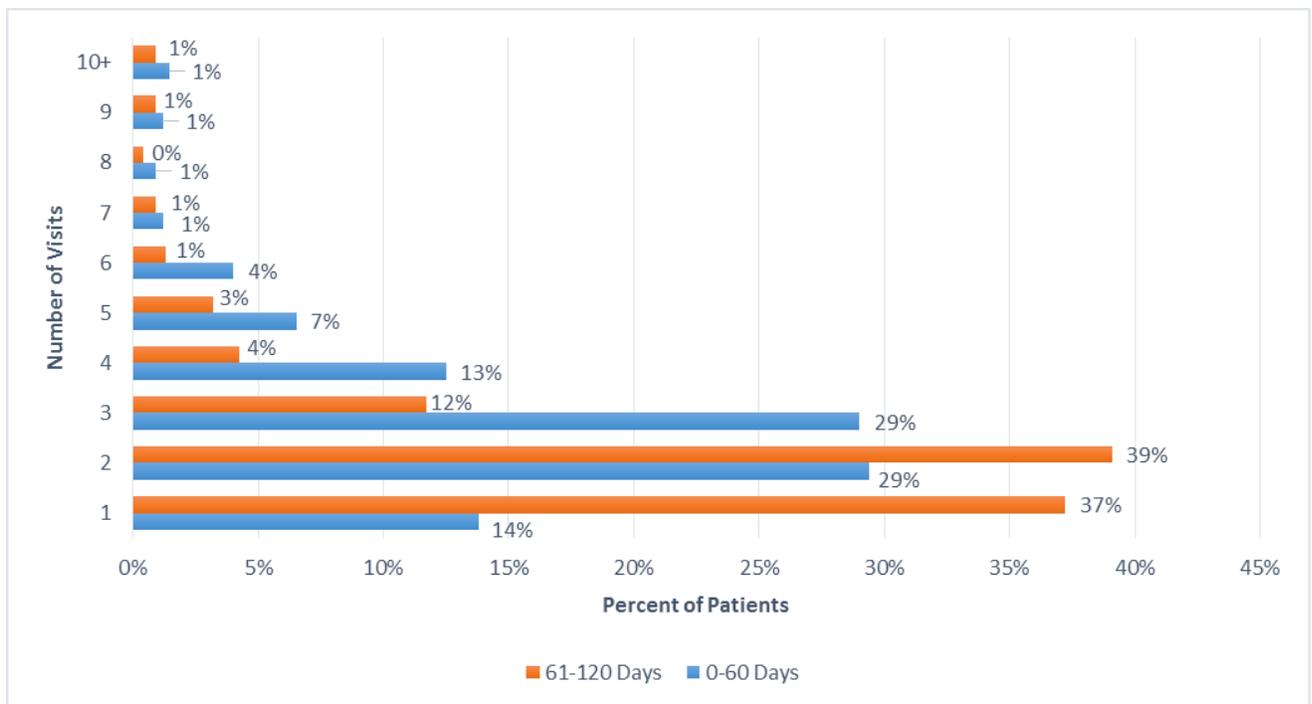
Note on boxplots: upper and lower hinges for each boxplot correspond to the 75th and 25th percentiles of each distribution, respectively. The upper and lower whiskers extend to the highest and lowest values that are within 1.5 x the interquartile range from the upper and lower hinges, respectively. Data 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.

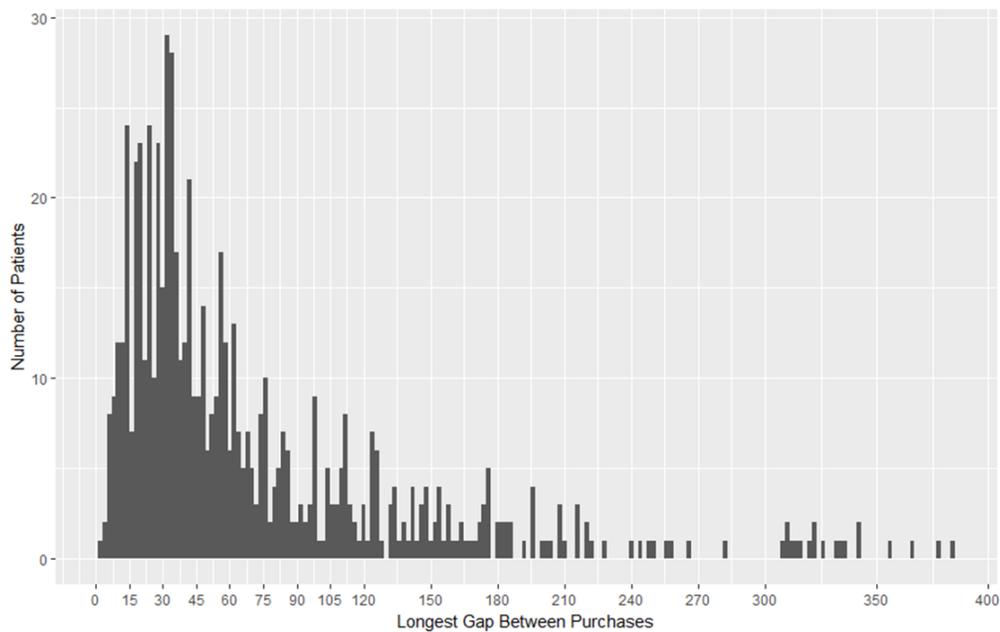


Patients Who Stopped Purchasing Medical Cannabis

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.

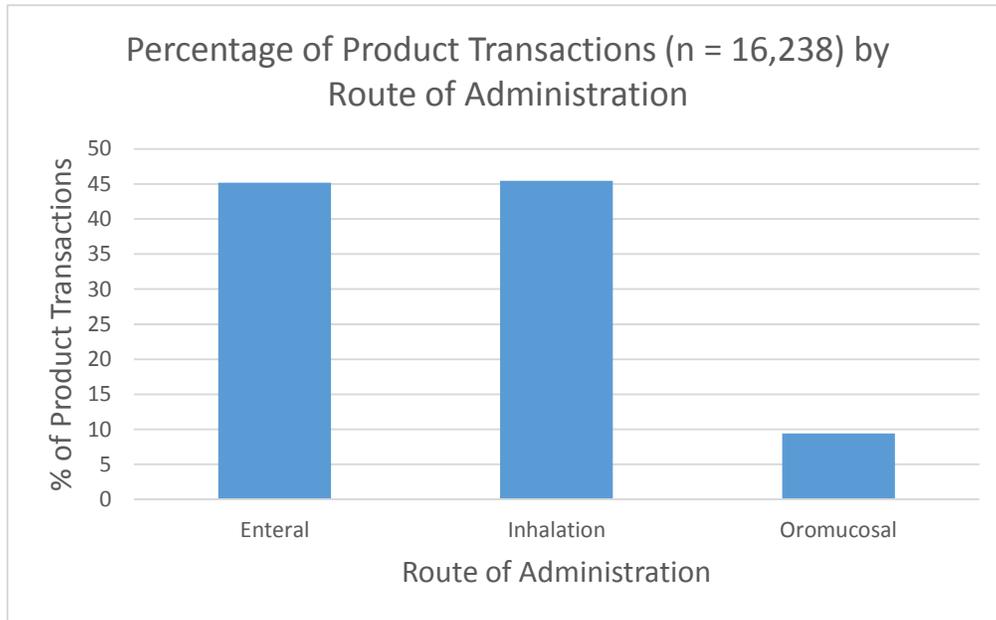
Box 5.1. Definitions to classify medical cannabis products by THC:CBD ratios.

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

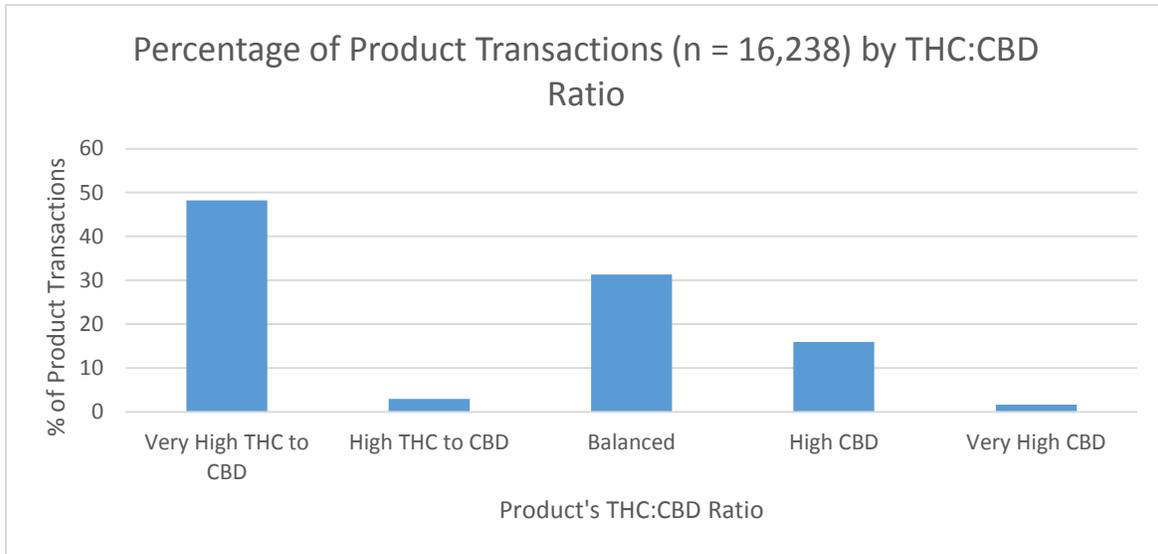
Products purchased for enteral administration (swallowed – includes capsules and oral solutions) and inhalation (vaporized oil) represented the majority of the products purchased (90.6% of all product transactions) with significantly fewer products purchased for oromucosal absorption (oil absorbed through 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).



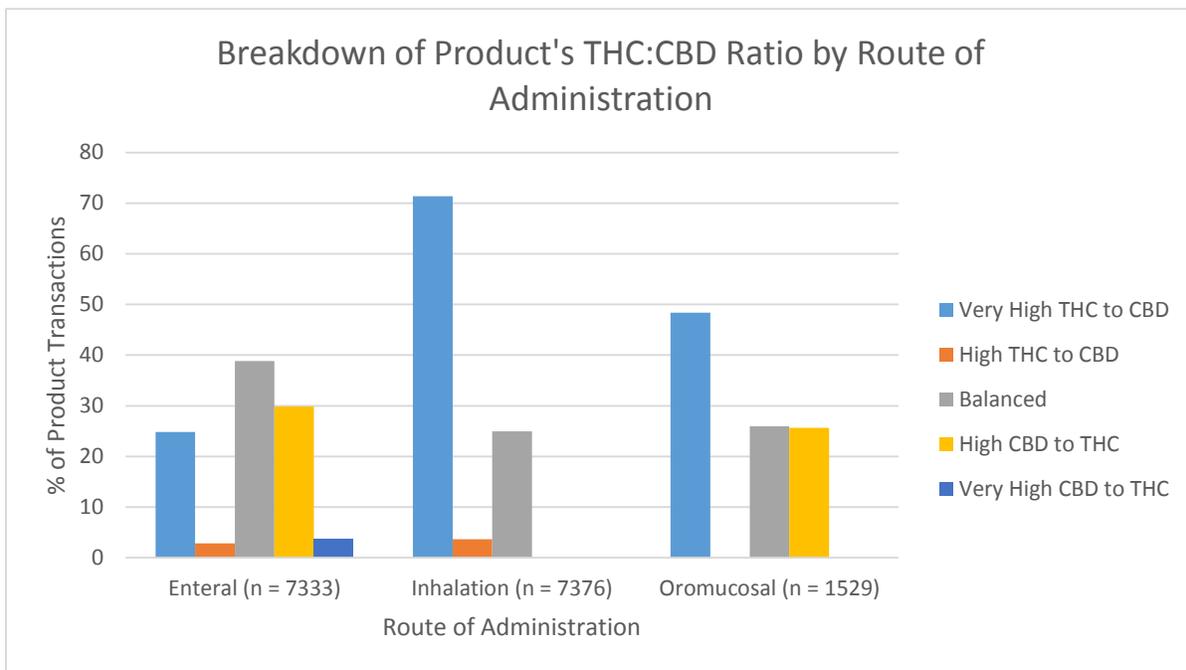
When products were classified by the ratio of THC to CBD present in the product, the following patterns emerged. Firstly, 48.2% of all product transactions were for products with very high THC amounts compared to CBD (hundreds to one). Balanced products (roughly equal amounts of THC to CBD) represented 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

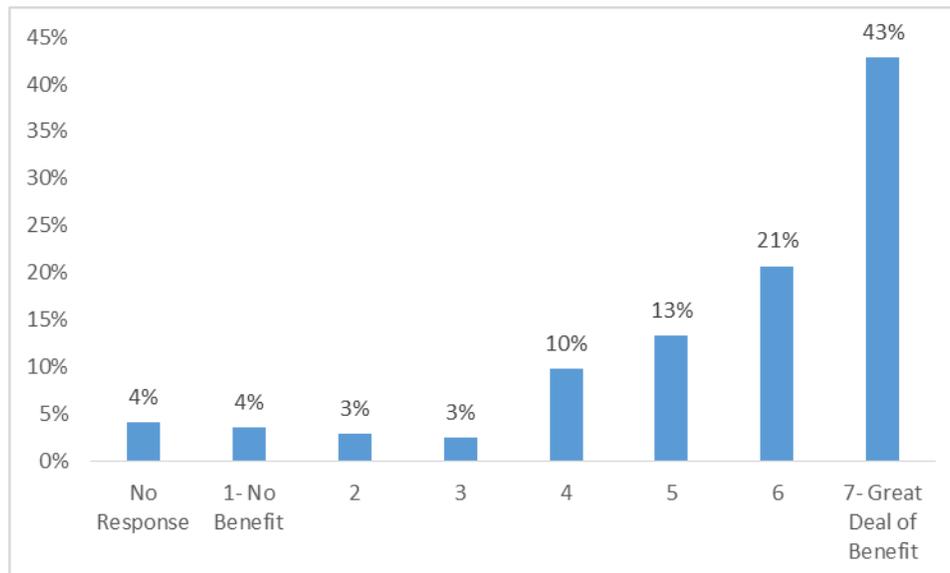
The Patient Experience and HCP surveys both ask respondents to report how much benefit they believe the patient received from using medical cannabis, on a scale from 1 (no benefit) to 7 (a great deal of benefit). Figures 6.1-6.10 show the distribution of benefit scores on this scale, as reported by patients, 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.

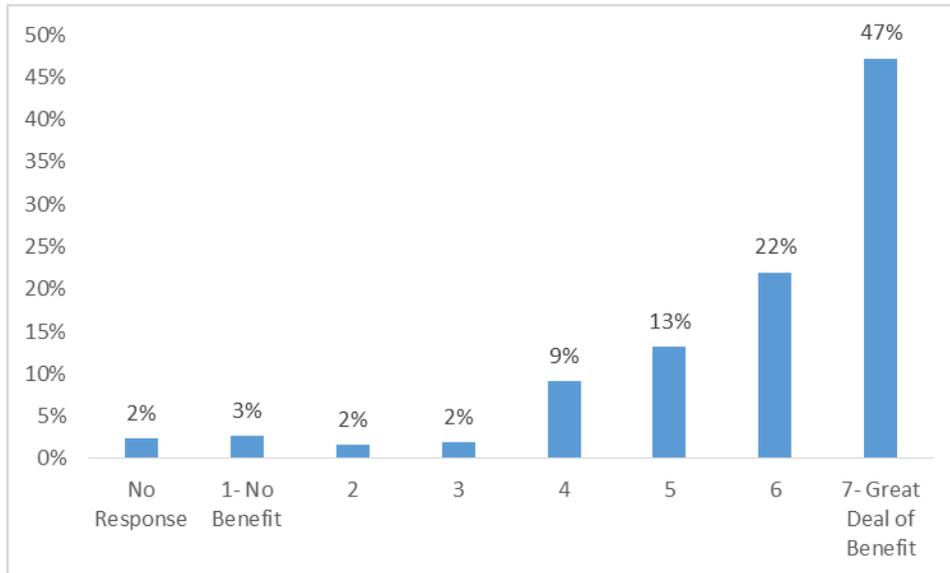
Figure 6.1. Patient-Perceived Benefit: All Conditions (N=792).



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.

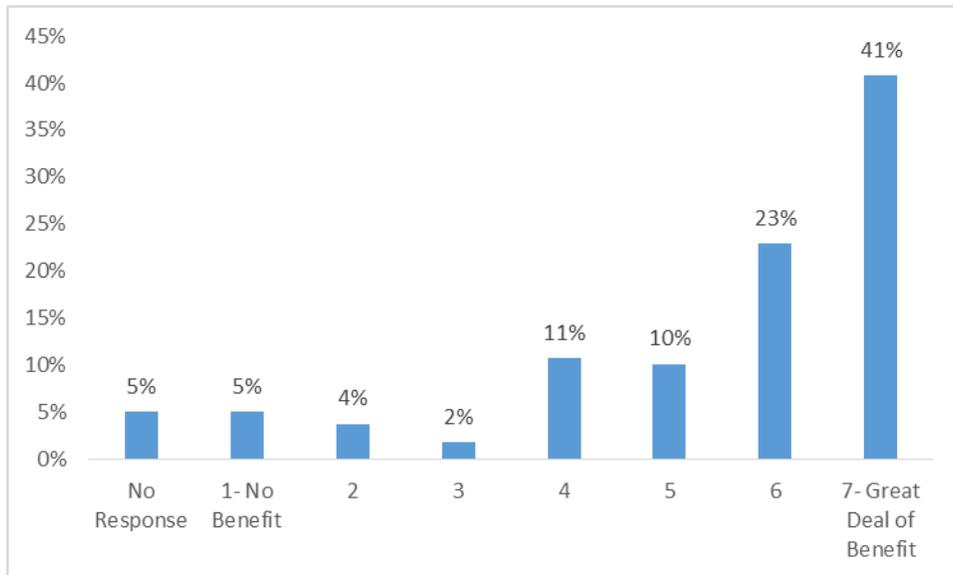
Figure 6.2. Patient-Perceived Benefit: Muscle Spasms (N=373)



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.

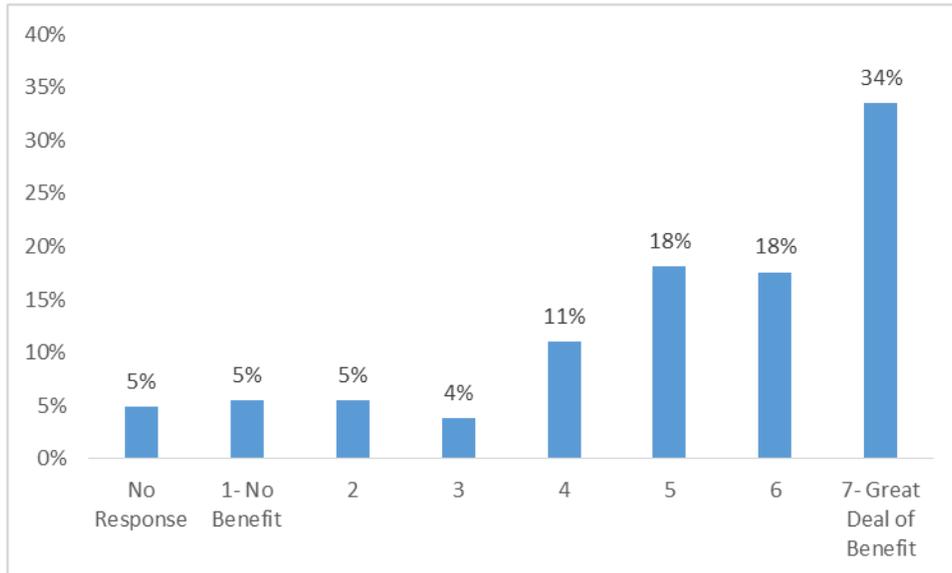
Figure 6.3. Patient-Perceived Benefit: Cancer (N=157)



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.

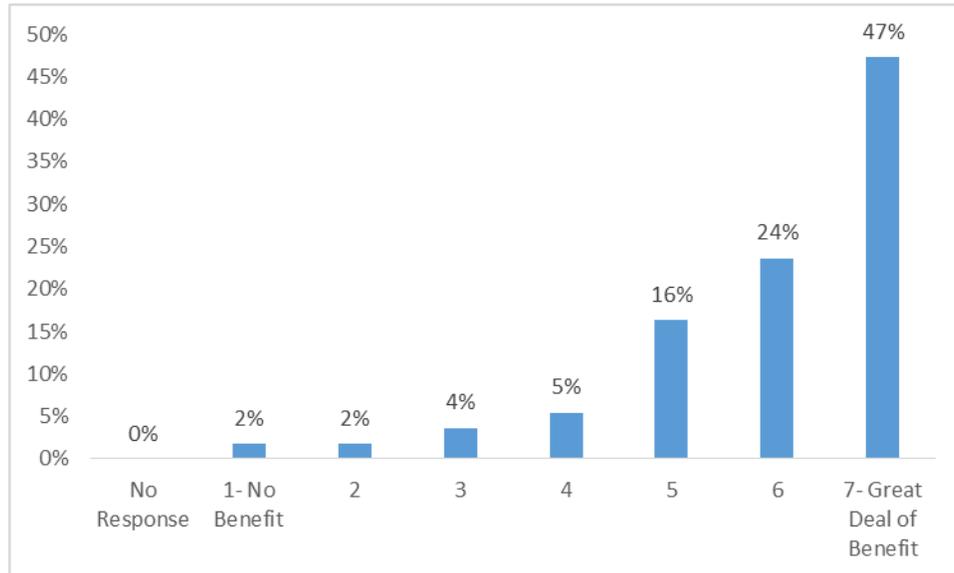
Figure 6.4. Patient-Perceived Benefit: Seizures (N=182)



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.

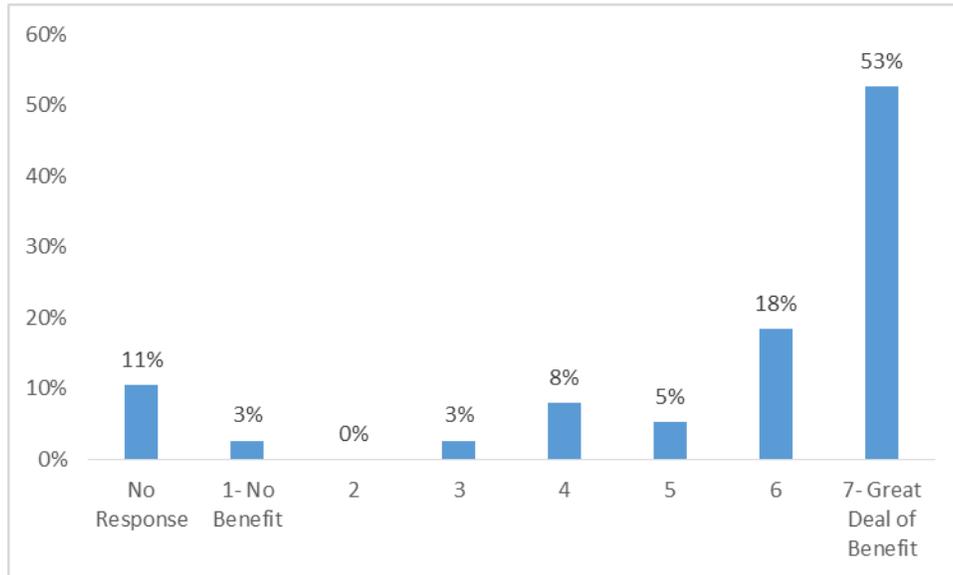
Figure 6.5. Patient-Perceived Benefit: Crohn's Disease (N=55)



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.

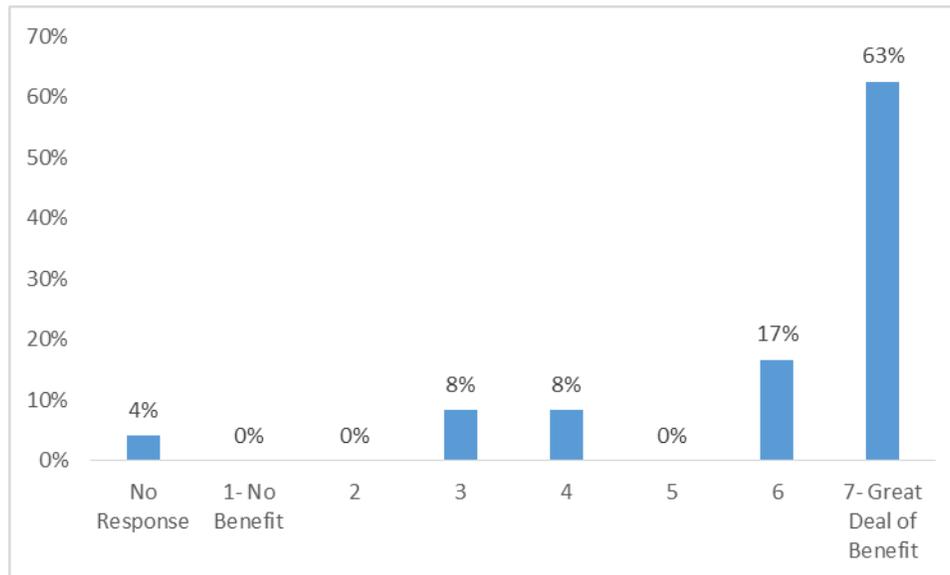
Figure 6.6. Patient-Perceived Benefit: Terminal Illness (N=38)



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.

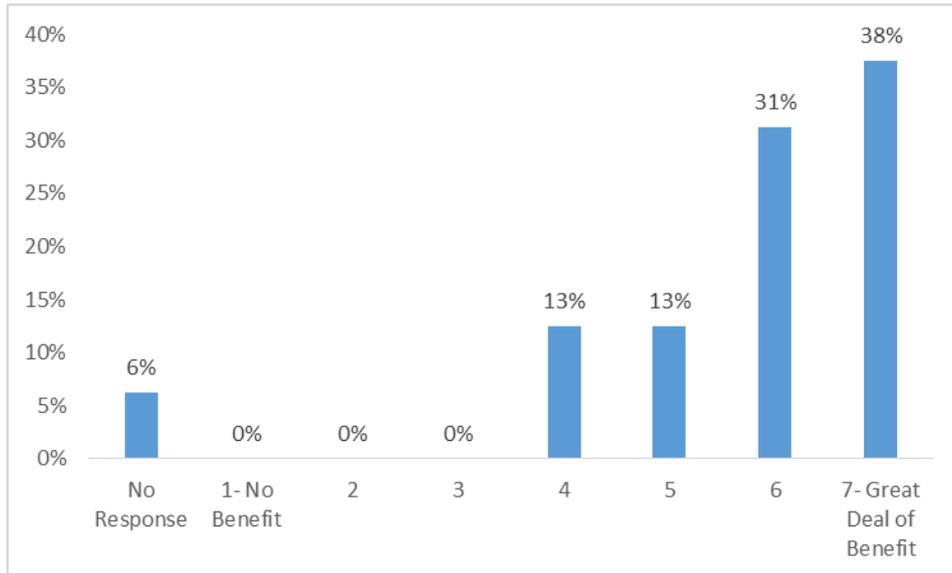
Figure 6.7. Patient-Perceived Benefit: HIV/AIDS (N=24)



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.

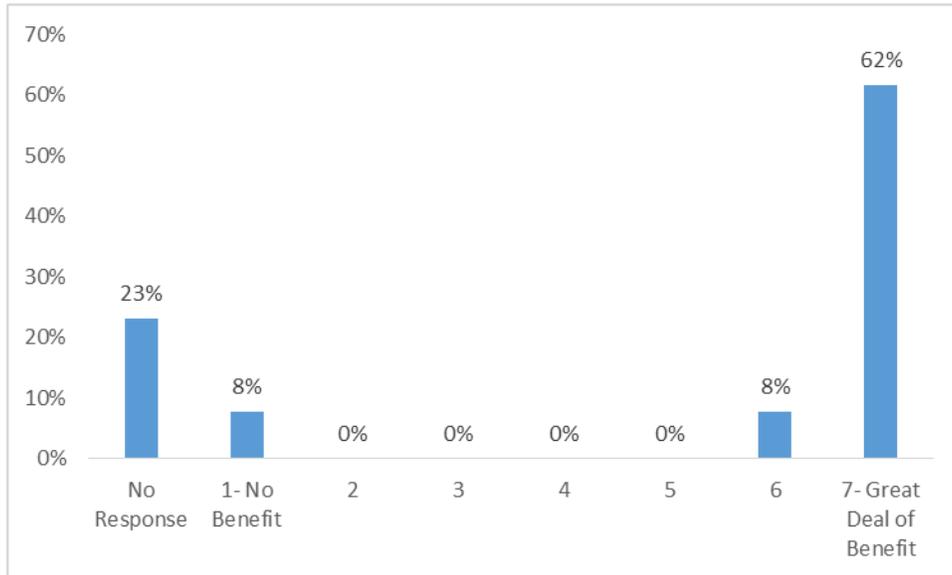
Figure 6.8. Patient-Perceived Benefit: Tourette Syndrome (N=16)



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.

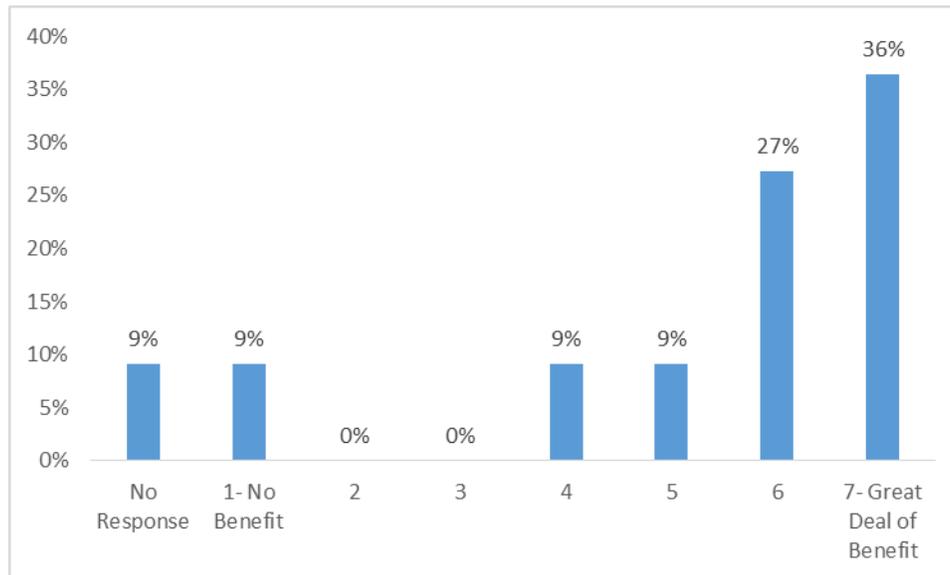
Figure 6.9. Patient-Perceived Benefit: Glaucoma (N=13)



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.)

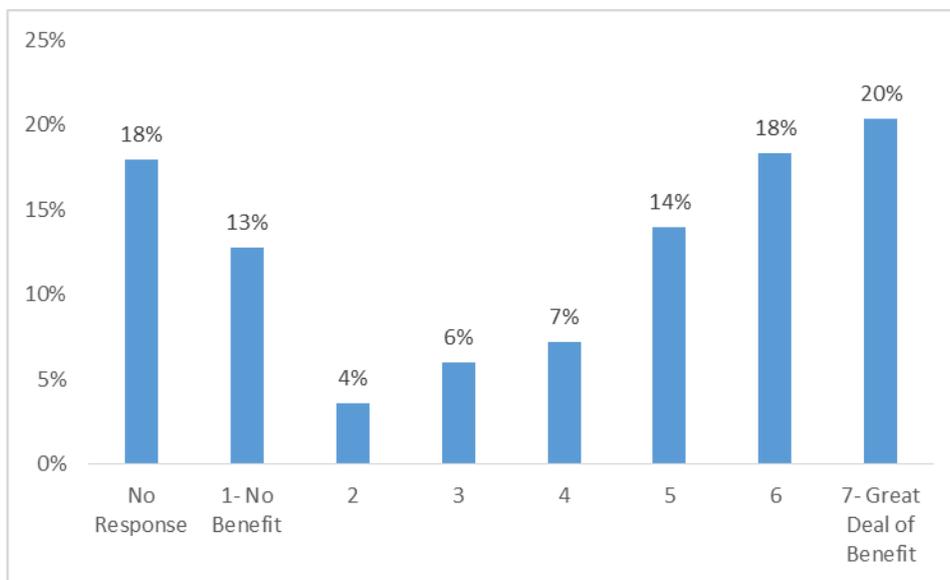
Note that results from patient surveys (Figures 6.1-6.10) and health care practitioner surveys (Figures 6.11-6.20) do not pertain to identical groups of patients. That is, some patients have

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.

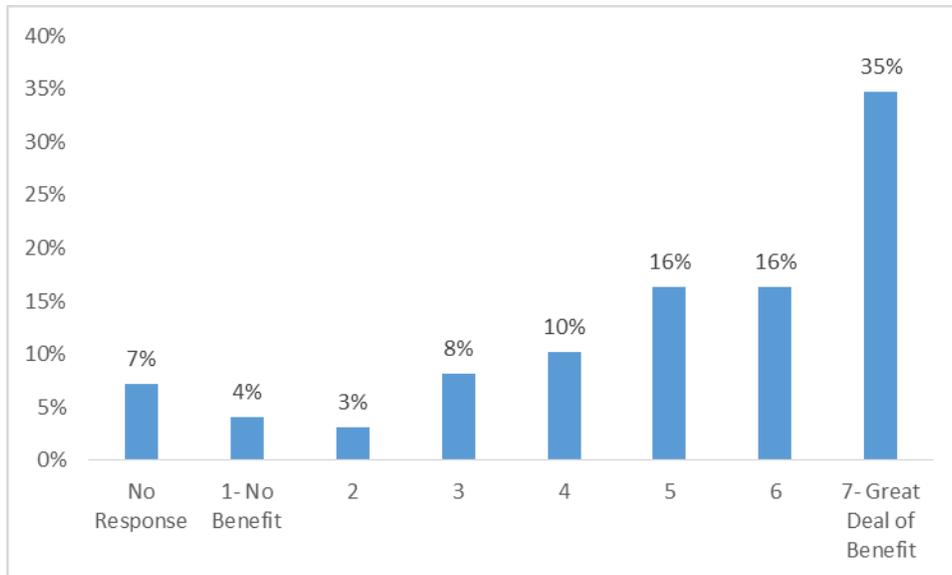
Figure 6.11. HCP-Perceived Benefit: All Conditions (N=251)



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.

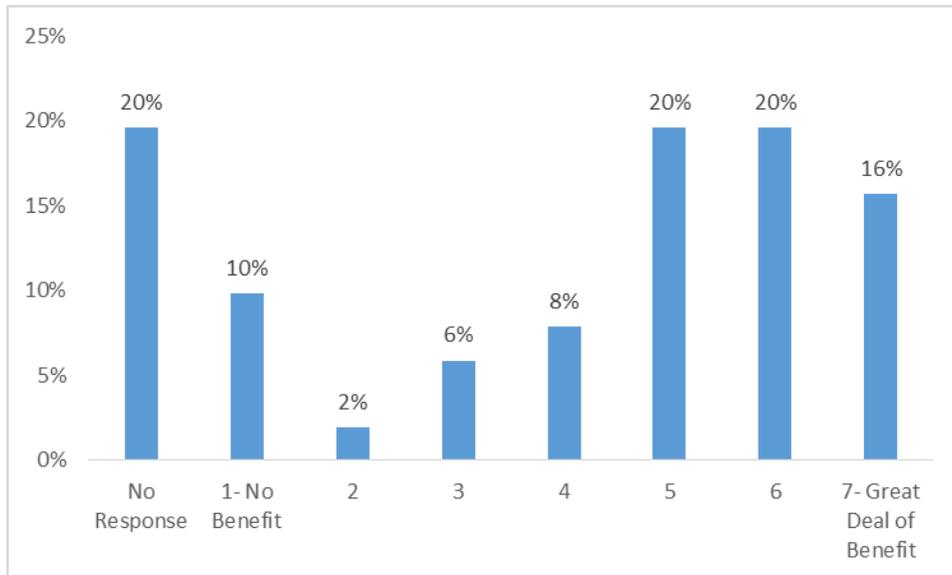
Figure 6.12. HCP-Perceived Benefit: Severe and Persistent Muscle Spasms (N=98)



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.

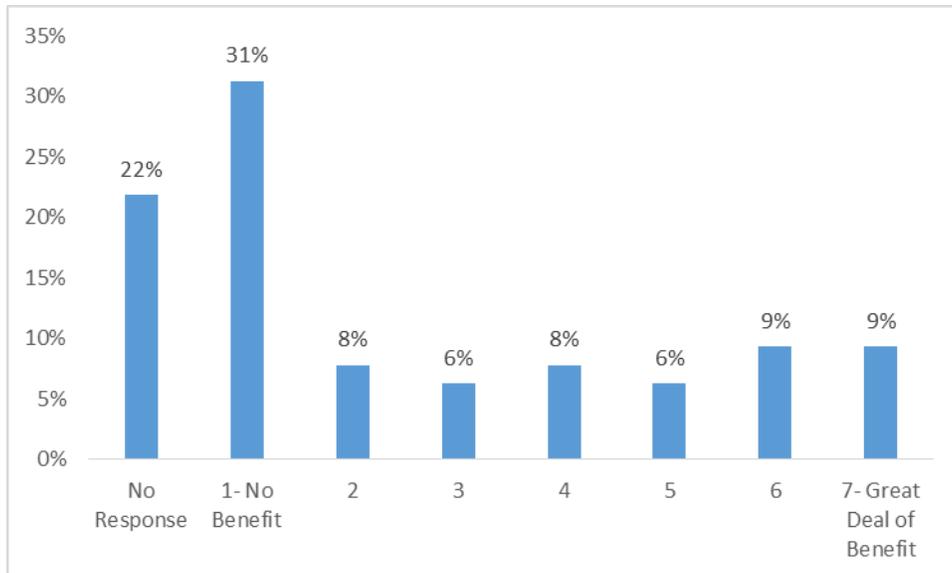
Figure 6.13. HCP-Perceived Benefit: Cancer (N=51)



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.

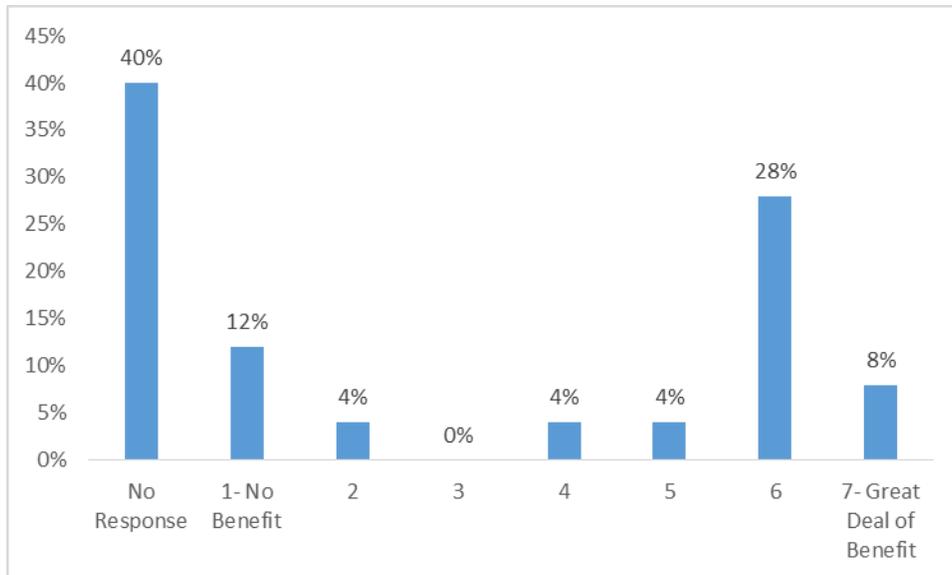
Figure 6.14. HCP-Perceived Benefit: Seizures (N=64)



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.

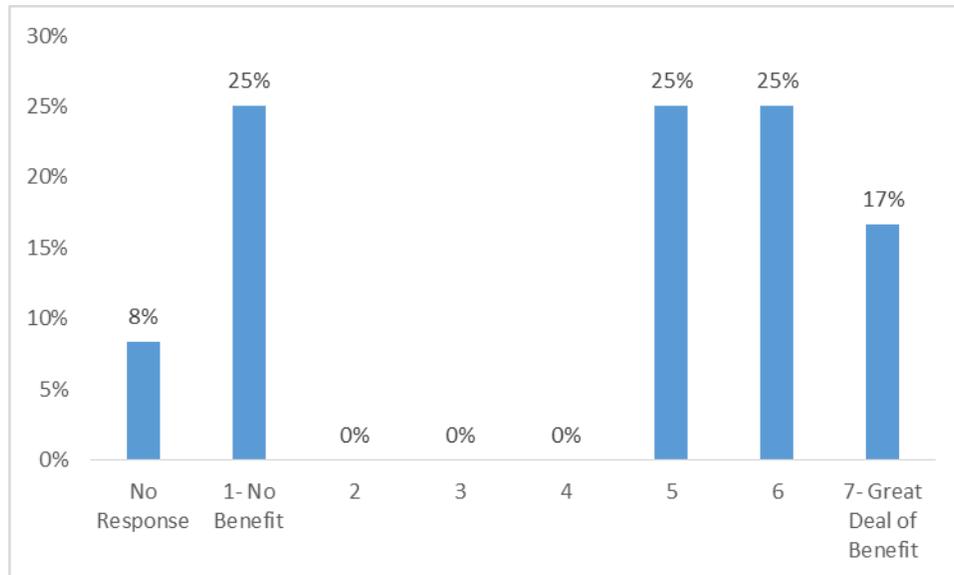
Figure 6.15. HCP-Perceived Benefit: Crohn's Disease (N=25)



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.

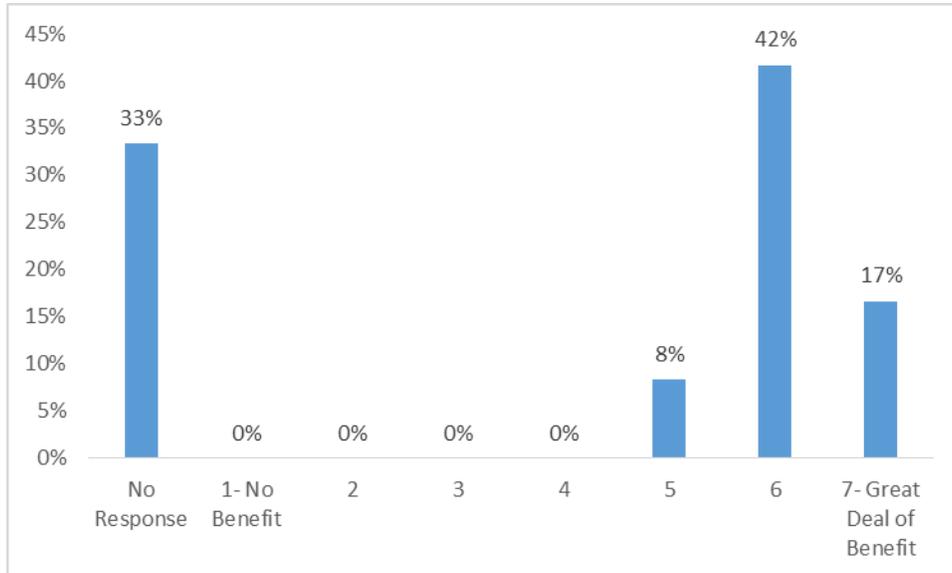
Figure 6.16. HCP-Perceived Benefit: Terminal Illness (N=12)



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.

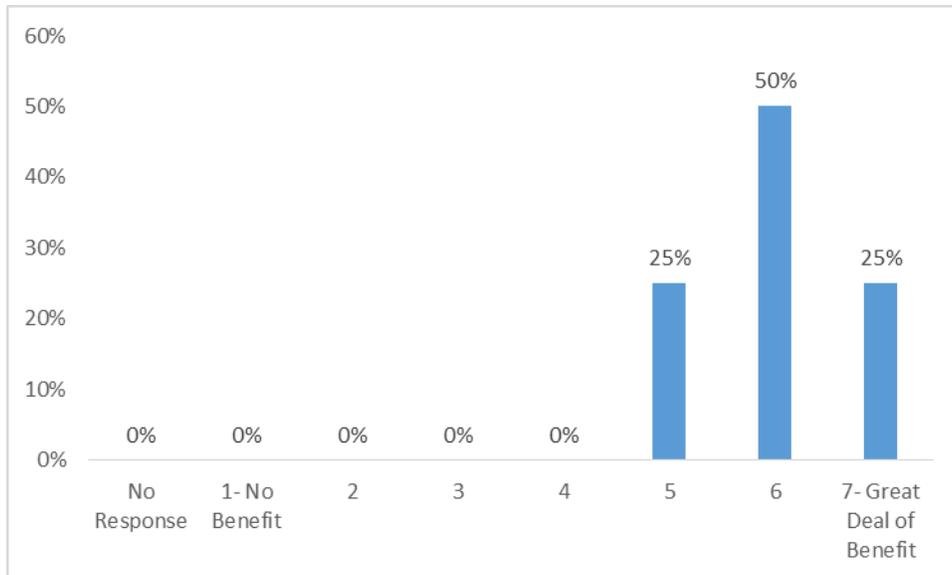
Figure 6.17. HCP-Perceived Benefit: HIV/AIDS (N=12)



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.

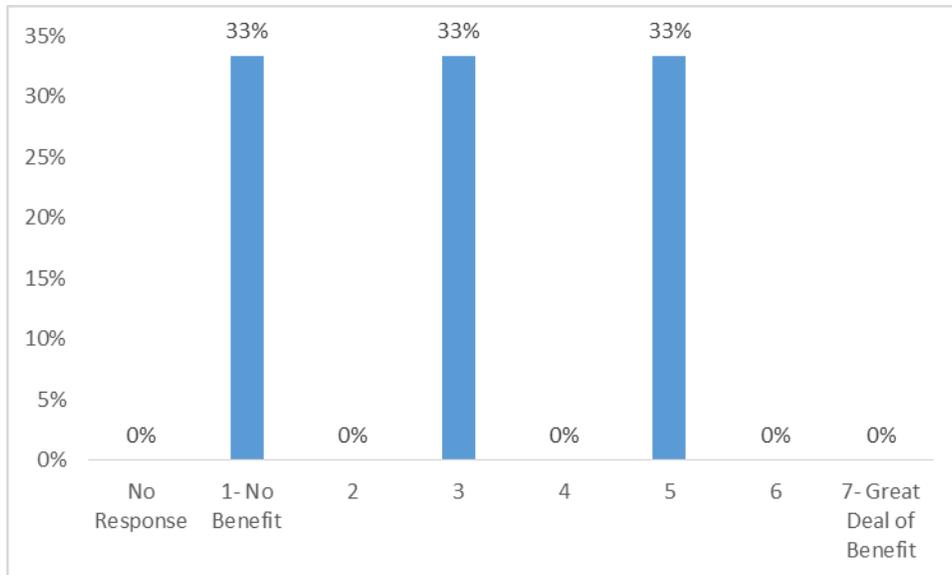
Figure 6.18. HCP-Perceived Benefit: Tourette Syndrome (N=4)



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.

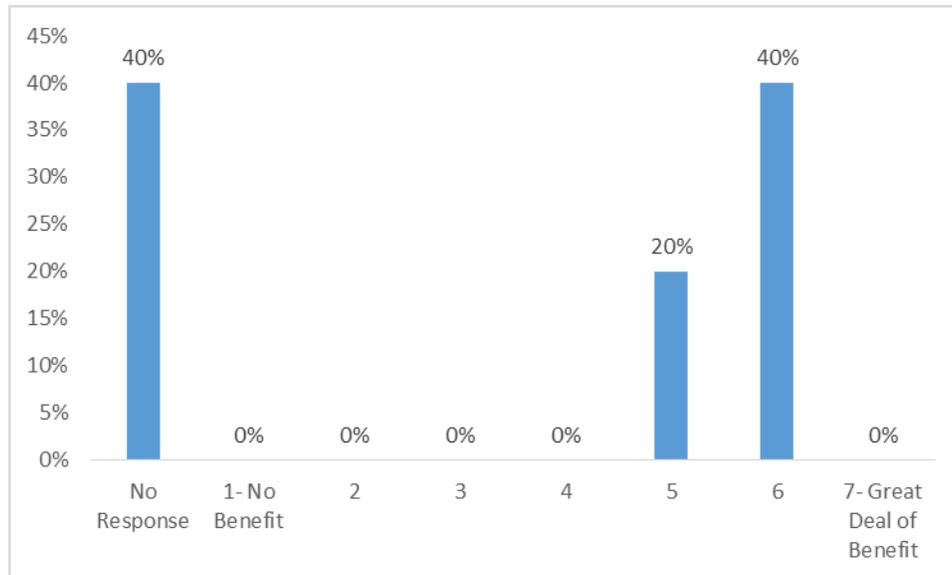
Figure 6.19. HCP-Perceived Benefit: Glaucoma (N=3)



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.

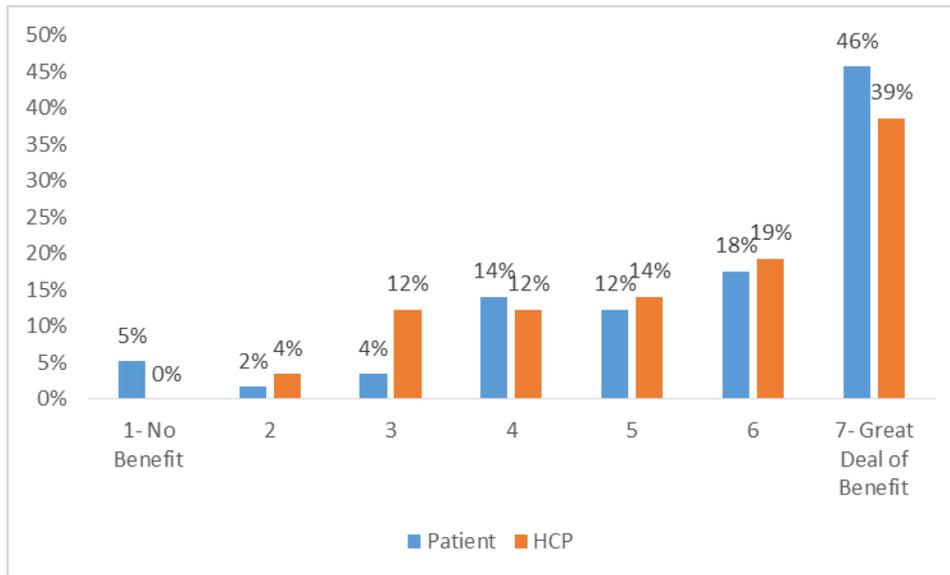
Table 6.13. Distribution of patient-reported benefits and HCP-reported benefits for patients with both patient and HCP surveys completed (n=126).

	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.

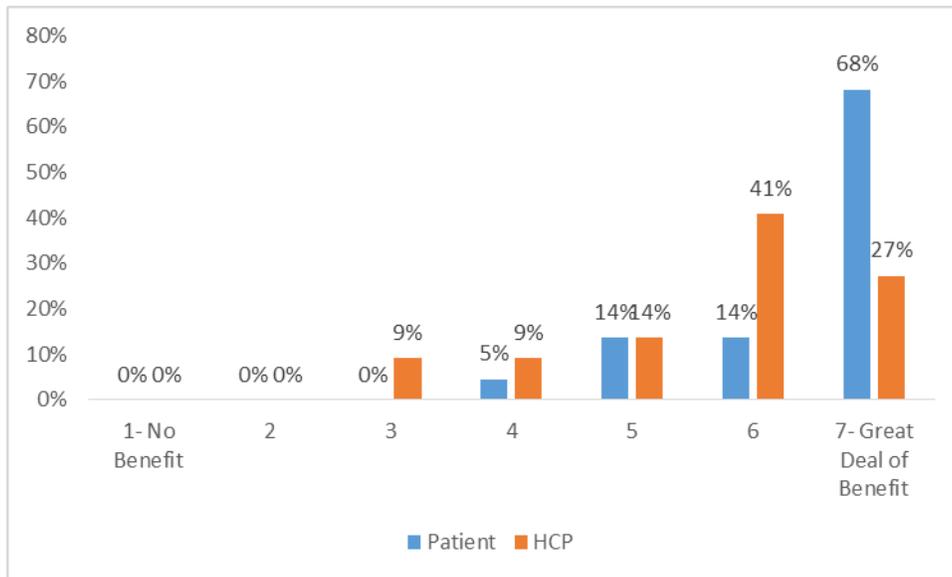
Figure 6.21. Muscle Spasms (N=57): Perceived Benefit



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.

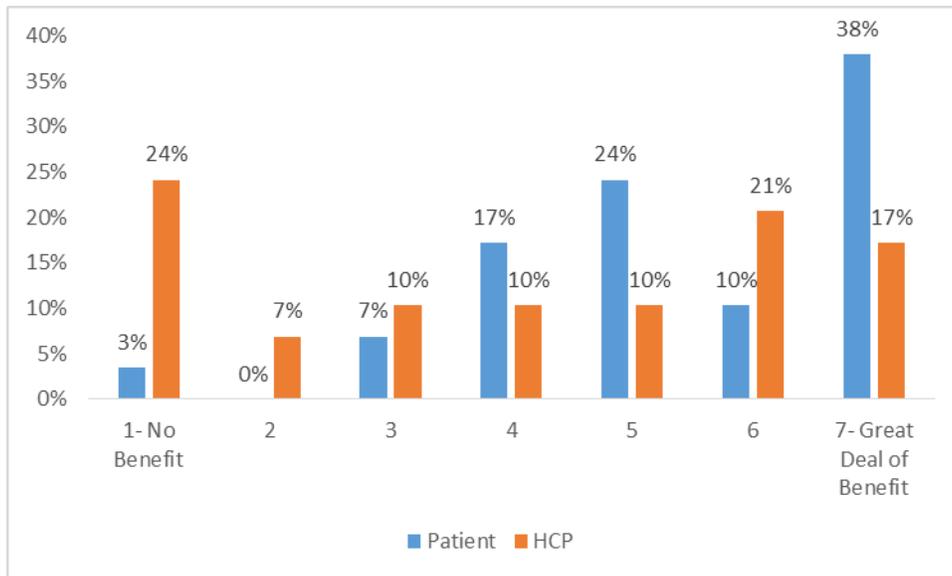
Figure 6.22. Cancer (N=22): Perceived Benefit



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.

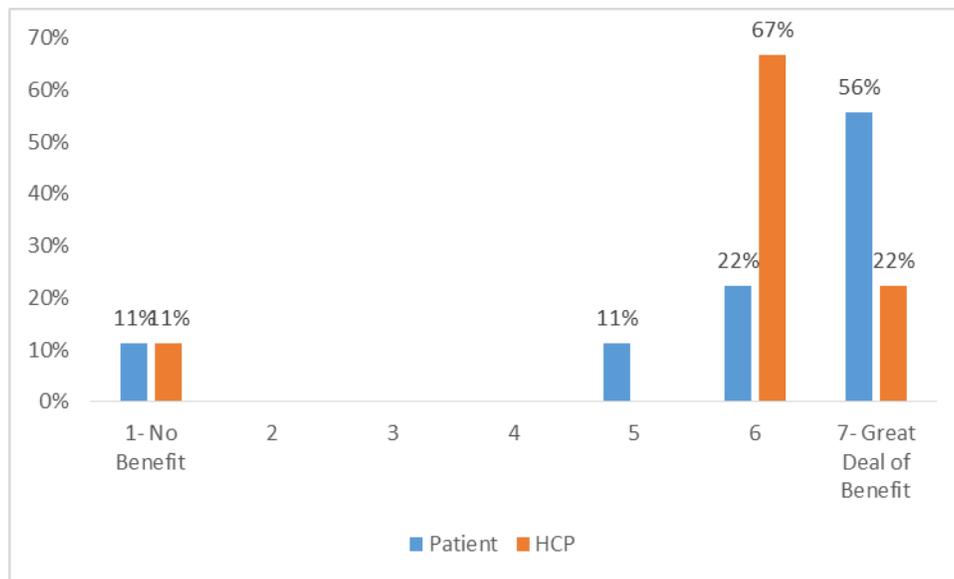
Figure 6.23. Seizures (N=29): Perceived Benefit



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



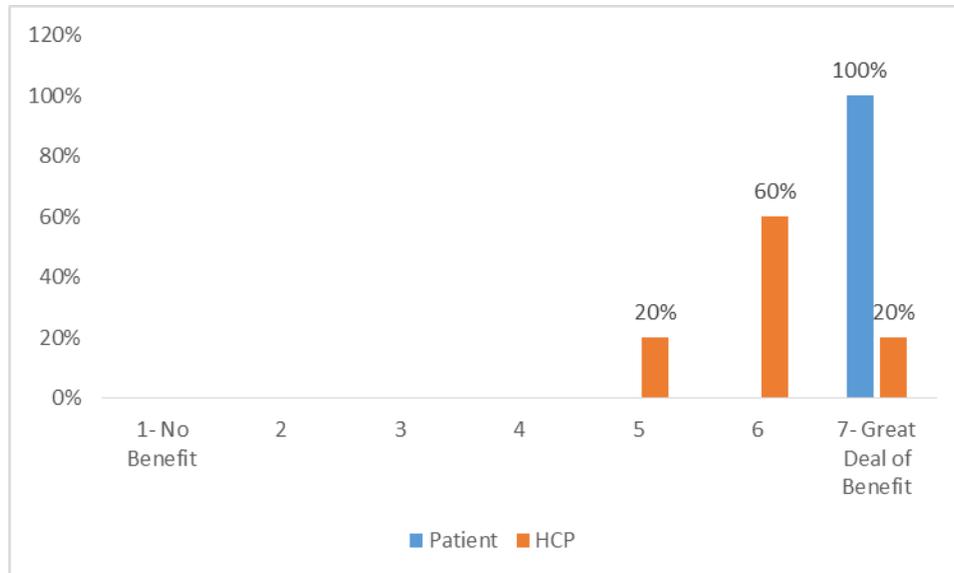
Terminal Illness

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.

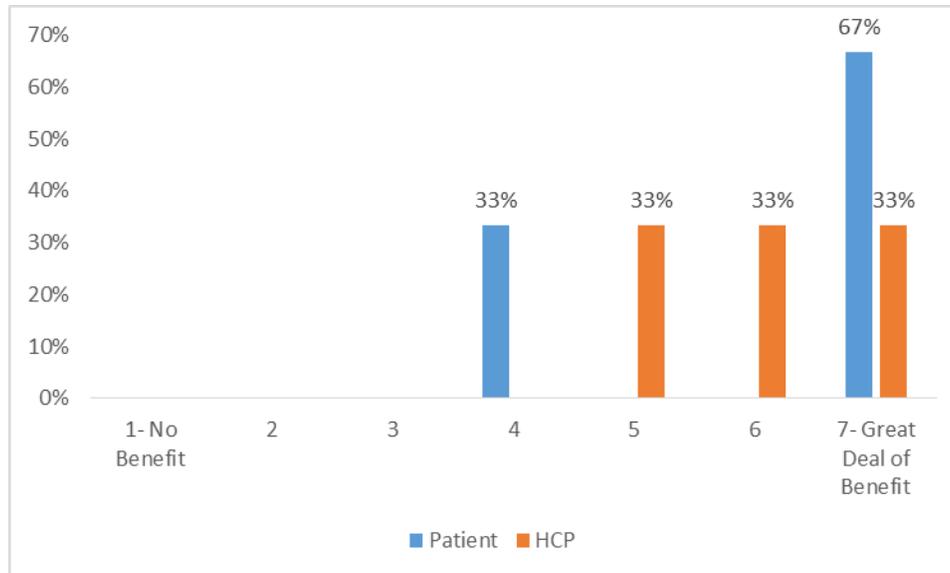
Figure 6.25. HIV/AIDS (N=5): Perceived Benefit



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.

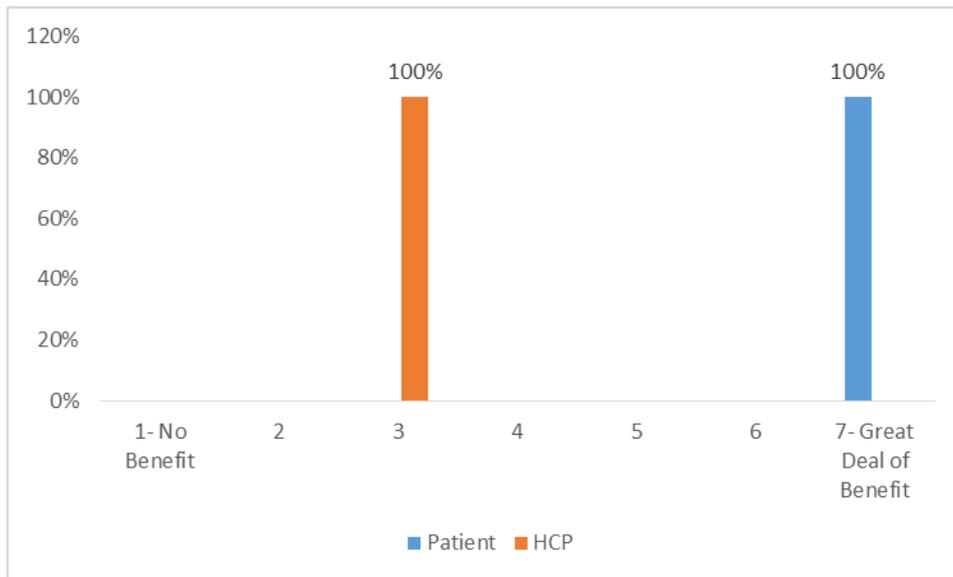
Figure 6.26. Tourette Syndrome (N=3): Perceived Benefit



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).

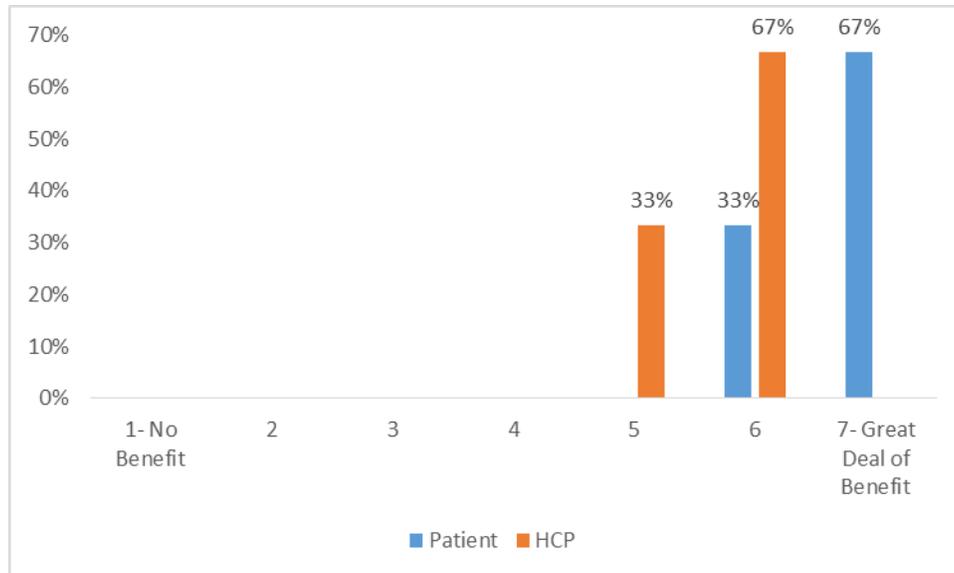
Figure 6.27. Glaucoma (N=1): Perceived Benefit



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).

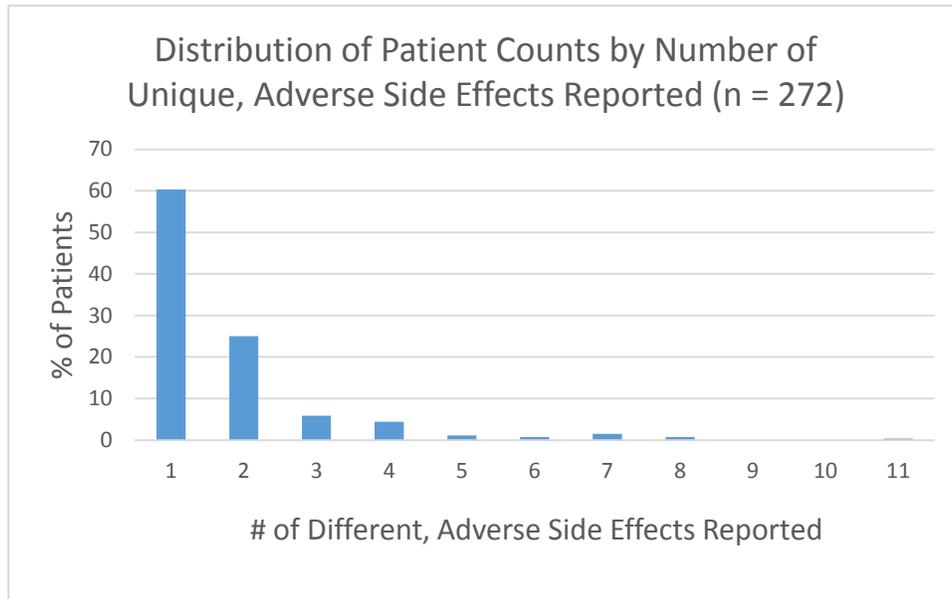


Figure 7.2 shows the percentage of patients reporting specific adverse side effects (Table 7.1 below lists adverse side effects that were reported by less than 2% of all patients). Of all side effects reported, dry mouth and drowsiness/somnolence/sedation were the most commonly reported side effects 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).

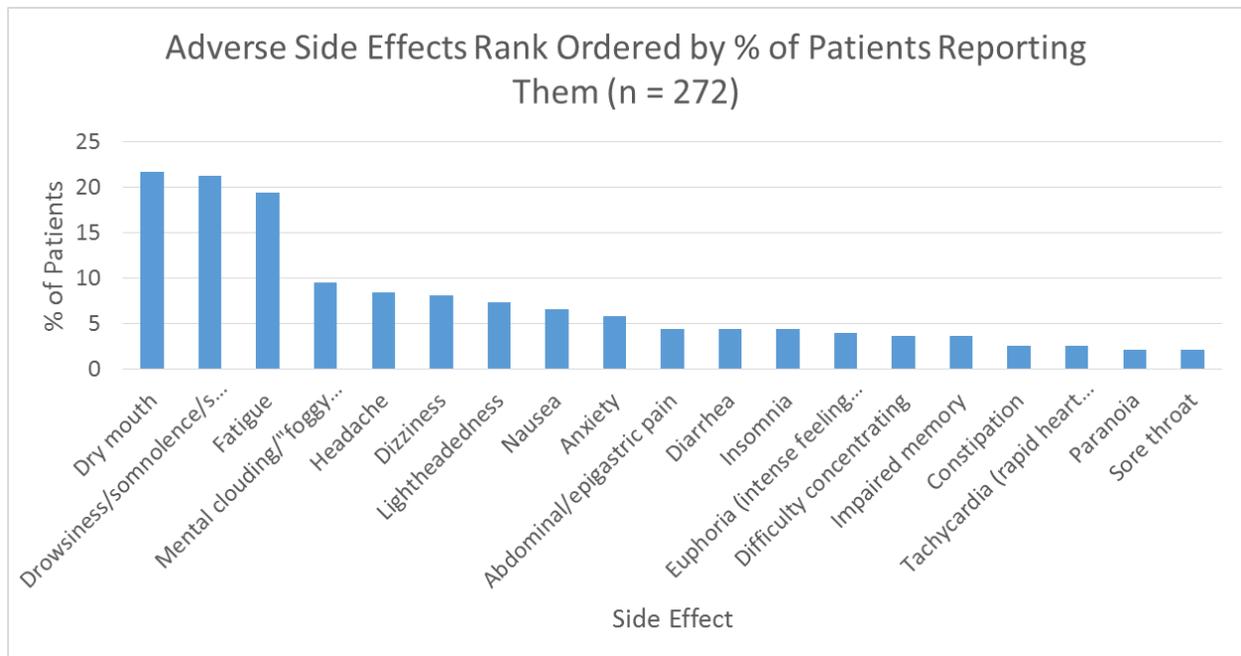


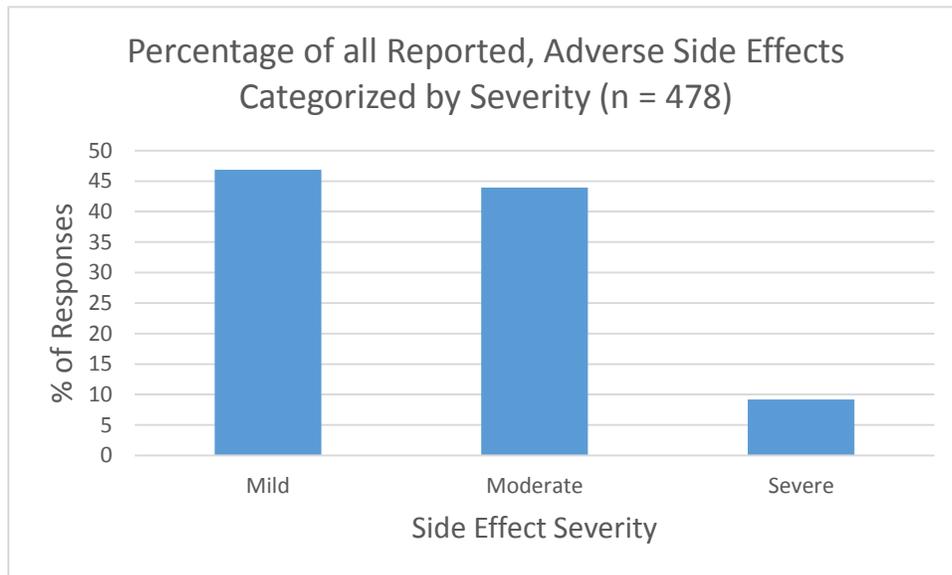
Table 7.1. Adverse side effects that were reported by less than 2% of patients (out of 272 patients).

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.

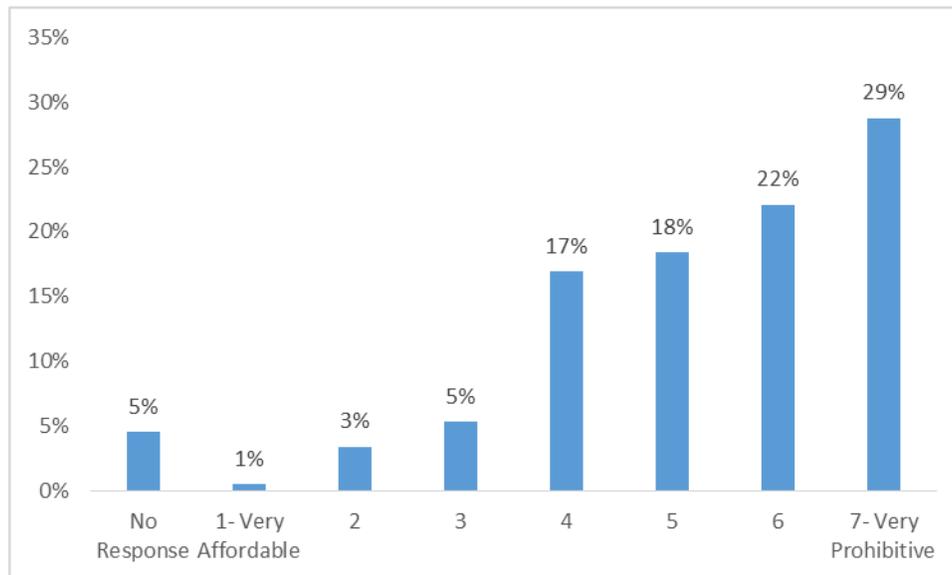
Patients, their registered caregivers, and certifying health care practitioners have a duty as program participants to report serious adverse events. Called “serious adverse incidents” in the program’s rules (4770.4002), these are essentially occurrences that lead to hospitalization or are life-threatening 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).

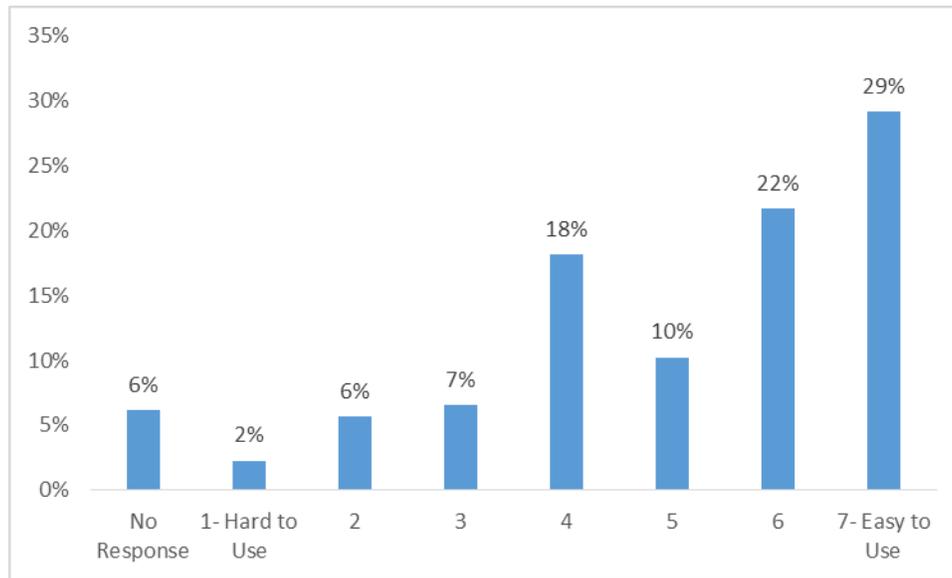
Figure 8.1. Patient Perceptions of Product Affordability



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

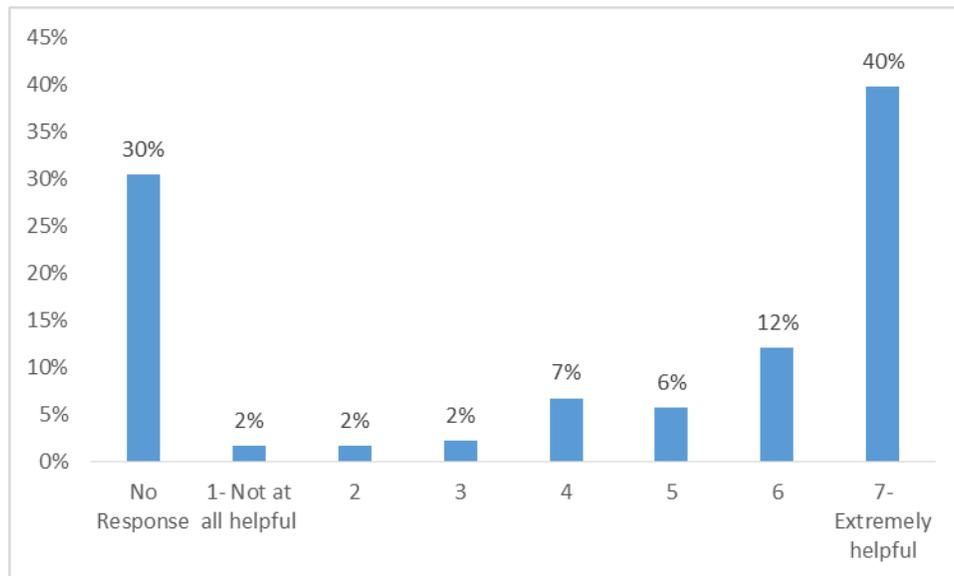


Patient reports on the ease of use of the Medical Cannabis Registry online system (1=very difficult to use; 4=neither difficult nor easy to use; 7=very easy/intuitive to use). Note: percentages are based on total number of patient responses; 49 patients did not complete this question and are not represented 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 as 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

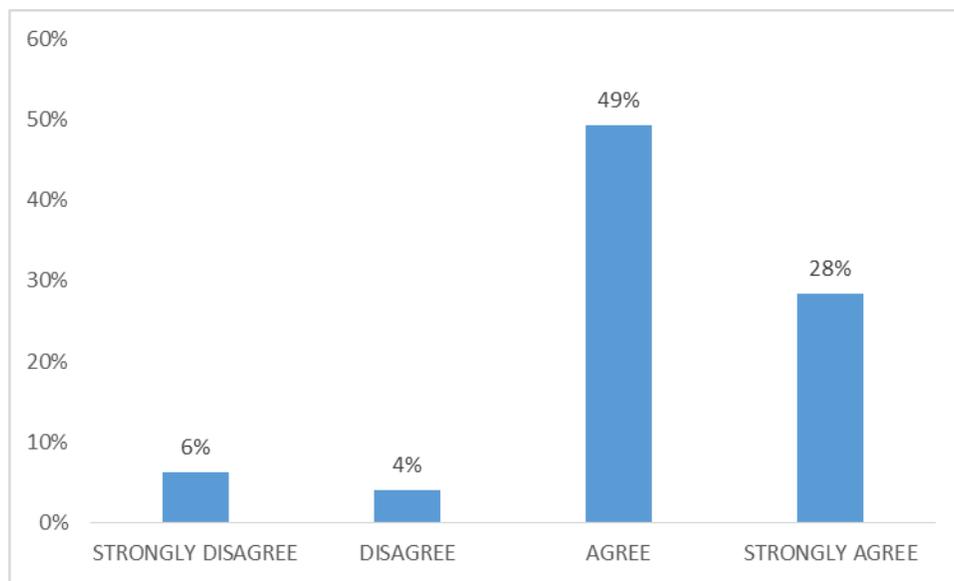


Patient reports on the helpfulness of the Office of Medical Cannabis Patient Support Center (1=not very helpful; 4=somewhat helpful; 7=very helpful). Note: percentages are based on total number of patient responses; 241 patients did not complete this question (several indicated no experience with the 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.

From: Condition Petition Tuesday, December 31,
To: 2019 5:12:55 PM [Question 2 GAD \(3\).pdf](#)
Subject: [Question 5 GAD \(2\).pdf](#)
Date:
Attachments:

This message was sent from the Condition page on medicalmarijuana.ohio.gov.

Box was check regarding file size being too large to upload. Action needed!

Name:
Address:
Phone:
Email:

Specific Disease or Condition:
Generalized Anxiety Disorder (GAD)

Information from experts who specialize in the disease or condition.
File larger than 3MB

Relevant medical or scientific evidence pertaining to the disease or condition.
See Attached

- Question 2 GAD (3).pdf

Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition.
File larger than 3MB

Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation.
File larger than 3MB

Letters of support provided by physicians with knowledge of the disease or condition. This may include a letter provided by the physician treating the petitioner, if applicable.
See attached file

- Question 5 GAD (2).pdf

Question 1

Information from experts who specialize in the disease or condition

Contents

Overview – 3

Generalized Anxiety Disorder: Prevalance, Burden, and Cost to Society - 4

Final Agency Decision: Petitions to Establish Additional Debilitating Medical Conditions Under the New Jersey Medicinal Marijuana Program – New Jersey Department of Health - 17

Overview

General Anxiety Disorder (GAD) is a debilitating condition that has proven difficult to treat. The burden created by GAD has been compared to that of major depression.

As recently as March of 2018, the New Jersey Department of Health determined that GAD and anxiety as a broader set of conditions are so debilitating, and evidence of medical marijuana's effectiveness so persuasive, that they add anxiety to the state's qualifying conditions list.

GAD has also been shown to have a significant impact on society at large. The social routines of patients suffering from GAD and those around them can be severely interrupted. Additionally, work productivity has been shown to decrease in those with GAD creating an economic consequence for society when treatment isn't adequate.

The attached documents seek to explain New Jersey's reasoning for adding anxiety as a qualifying condition and explain the burden of GAD.

Research Article

GENERALIZED ANXIETY DISORDER: PREVALENCE, BURDEN, AND COST TO SOCIETY

Hans-Ulrich Wittchen, Ph.D.*

Generalized anxiety disorder (GAD) is a prevalent and disabling disorder characterized by persistent worrying, anxiety symptoms, and tension. It is the most frequent anxiety disorder in primary care, being present in 22% of primary care patients who complain of anxiety problems. The high prevalence rate of GAD in primary care (8%) compared to that reported in the general population (12-month prevalence 1.9–5.1%) suggests that GAD patients are high users of primary care resources. GAD affects women more frequently than men and prevalence rates are high in midlife (prevalence in females over age 35: 10%) and older subjects but relatively low in adolescents. The natural course of GAD can be characterized as chronic with few complete remissions, a waxing and waning course of GAD symptoms, and the occurrence of substantial comorbidity particularly with depression. Patients with GAD demonstrate a considerable degree of impairment and disability, even in its pure form, uncomplicated by depression or other mental disorders. The degree of impairment is similar to that of cases with major depression. GAD comorbid with depression usually reveals considerably higher numbers of disability days in the past month than either condition in its pure form. As a result, GAD is associated with a significant economic burden owing to decreased work productivity and increased use of health care services, particularly primary health care. The appropriate use of psychological treatments and antidepressants may improve both anxiety and depression symptoms and may also play a role in preventing comorbid major depression in GAD thus reducing the burden on both the individual and society. Depression and Anxiety 16:162–171, 2002. © 2002 Wiley-Liss, Inc.

Key words: *generalized anxiety disorder; prevalence; health care utilization; comorbidity*

INTRODUCTION

Generalized anxiety disorder (GAD) is a persistent and often severe mental disorder of the anxiety spectrum, characterized by persistent (6 months or more), excessive worrying, anxiety, tension associated with symptoms of hypervigilance, and other somatic symptoms of anxiety. The symptomology is associated with substantial and enduring subjective suffering, and the feeling of loss of control over the worrying and symptoms as another criterion. Clinical reports suggest that fewer than 20% of sufferers experience complete remission of their symptoms, and typically patients will have had their symptoms for between 5 and 10 years before they are diagnosed and effectively treated [Ballenger et al., 2001; Kessler et al., 2001a; Rogers et al., 1999]. Patients with GAD have been found to be frequent utilizers of primary care resources rather than

mental health specialist settings and have been associated with over-utilization of general health care resources [Maier et al., 2000; Roy-Byrne and Katon, 1997; Wittchen et al., 2000; Wittchen et al., 2002]. Further primary care studies conducted in the early

Institute of Clinical Psychology and Psychotherapy, Technical University of Dresden, Germany and Max Planck Institute of Psychiatry, Munich, Germany

* Correspondence to: Professor Dr. Hans-Ulrich Wittchen, Max Planck Institute of Psychiatry, Clinical Psychology and Epidemiology Unit, Kraepelinstrasse 2, Munich D-80804, Germany. E-mail: wittchen@pipsykl.mpg.de

Received for publication 1 October 2001; Accepted 24 February 2002

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/da.10065

1990s have suggested that GAD is rarely recognized and diagnosed, and if it is diagnosed it is usually not, or only inappropriately, treated [Üstün and Sartorius, 1995]. This is particularly significant as GAD is associated with a substantial degree of social disability [Wittchen et al., 2000].

Yet, there has been some debate concerning the nosological status of GAD because of past reports of its low diagnostic reliability using standard criteria [DiNardo et al., 1993] and the fact that clinical studies have found that GAD is usually seen in comorbid presentations with major depression. Furthermore, there have been reports that pure GAD is both an extremely rare phenomenon with few indications of disorder-specific impairments (for examples, see discussions in Kessler et al., 2001a; Noyes et al., 2001). However, one needs to take into account that these reservations against GAD, being an independent clinical disorder of critical significance, are based on studies that have mostly used older diagnostic criteria for GAD and/or stem from highly selective clinical samples that might suffer considerable selection bias.

Since the current diagnostic definition of GAD is a relatively recent addition to diagnostic classification systems, few studies have up to now reconsidered the nature and true burden of GAD, as defined by the current DSM-IV criteria, on the individual and society. This paper aims to address the question “what is the prevalence, level of disability and burden to society associated with GAD, as defined by DSM-IV criteria?”

PREVALENCE

The concept and diagnostic criteria of GAD have changed significantly since it was first codified in the Diagnostic and Statistical Manual of Mental Disorders [American Psychiatric Association, 1994] in 1980 and to date there are still small differences in the criteria used in the USA and Europe. In the USA and in research, the DSM-III-R/DSM-IV criteria prevail, whereas in Europe the use of the 10th International Classification of Diseases [ICD-10; World Health Organization (WHO) 1992], which has broader criteria, is preferred at least in routine clinical settings. However, it is remarkable that despite the many changes in diagnostic criteria and the differences between these two diagnostic classification systems, the reported lifetime prevalence rates for GAD are remarkably consistent. This is in contrast to the considerable variance observed with other psychiatric disorders, such as depression and phobias.

COMMUNITY STUDIES

The US National Comorbidity Survey [NCS; Kessler et al., 1994] and the German National Health Interview and Examination Survey, Mental Health Supplement [GHS; Carter et al., 2001; Jacobi et al., 2002] are the largest community epidemiological studies of GAD to date. and, together, include over

TABLE 1. Twelve-month and lifetime prevalence in the NCS of GAD in males and females by age group [Wittchen et al., 1994]

Age (yr)	Male (%)	Female (%)	Total (%)
12-month prevalence			
15–24	1.3	1.5	1.4
25–34	3.2	5.0	4.1
35–44	2.3	4.5	3.4
≥45	0.9	6.3	3.5
Total	2.0	4.3	3.1
Lifetime prevalence			
15–24	1.5	2.5	2.0
25–34	4.7	7.1	6.0
35–44	4.6	7.2	5.9
≥45	3.6	10.3	6.9
Total	3.6	6.6	5.1

69,400 patients. The 12-month and lifetime prevalence rates of GAD (DSM-III-R) in the NCS were estimated to be 3.1% and 5.1%, respectively. The lowest lifetime prevalence rate was found in the 15–24 year age group (2.0%), while the highest rate was reported for the 45–55 year age group (6.9%) [Table 1; Wittchen et al., 1994]. This survey also demonstrated that women were twice as likely to have GAD than their male counterparts, with total lifetime prevalence rates of 6.6% and 3.6%, respectively [Wittchen et al., 1994]. The prevalence rate increased to 10.3% for women aged ≥45 years, but was unchanged for men aged ≥45 years (3.6%).

These findings are relatively consistent with findings from a previous GAD community survey that used earlier diagnostic criteria and different instruments [see review by Carter et al., 2001]. The most recent epidemiological study using DSM-IV criteria [GHS; Carter et al., 2001] has reported slightly lower 12-month prevalence rates for GAD than the NCS (12-month prevalence 1.5% vs. 3.1%). However, this finding was found to be entirely due to methodology because the inclusion of subjects with lifetime GAD and partially remitted subthreshold GAD accounts for this difference. The highest rates were again found in women and older subjects [Carter et al., 2001].

Although in the past there was some speculation about GAD being a characterological disorder [Akiskal, 2001] being best grouped under DSM axis II personality disorders, there has been little supporting evidence to date. Reports concerning the prevalence of GAD as defined by the DSM-III-R and the more stringent DSM-IV criteria in children and adolescents have generally found low rates of GAD in this age group [Müller, 2001, doctoral dissertation; Wittchen et al., 1998]. The prospective-longitudinal 5-year Early Developmental Stages of Psychopathology (EDSP) study in adolescents and young adults [Wittchen et al., 1998], which to our knowledge is the only DSM-IV-based study of this sort, examined the prevalence of GAD and patterns of age of onset among subjects aged

14–24 years at intake. This study found that GAD is rare in children and adolescents and that unlike most anxiety disorders, onset of GAD before the age of 25 years was uncommon. These findings are in agreement with those of most of the previous adult studies that report age of first onset data as well as surveys in children.

PRIMARY CARE

There is consistent evidence that patients with GAD are highly prevalent in primary care settings [Ormel et al., 1994; Schonfeld et al., 1997]. The international WHO multi-center study on Psychological Problems in General Health Care (PPGHC) assessed GAD using ICD-10 criteria with the Composite International Diagnostic Interview [CIDI; WHO, 1991] and estimated the current prevalence of GAD across centers to be approximately 8% of all primary care attenders [Üstün and Sartorius, 1995]. This was confirmed in a more recent reanalysis [Maier et al., 2000]. Of those patients visiting primary care physicians for a psychological problem, 25% presented with pure GAD in the absence of any comorbid psychiatric disorder [Maier et al., 2000]. In a subset of almost 2,000 individuals attending five of the European centers in this study [Weiller et al., 1998], 22% of all primary care patients who complained of any anxiety problems were found to have GAD. In this analysis, the overall current prevalence of GAD among primary care attenders was 8.5% with a further 4.1% of individuals having sufficient clinical problems to justify a diagnosis of subthreshold GAD.

The most recent primary care study of over 500 primary care centers and over 20,000 primary care attenders (Generalised Anxiety Disorder and Depression in Primary Care [GAD-P] study) has confirmed these findings on the basis of DSM-IV criteria for GAD [Hoyer et al., 2001; Wittchen et al., 2001; Wittchen et al., 2002]. The point prevalence of threshold GAD was estimated to be 5.3%, with highest estimates in those primary care attenders aged 35–60 years. The study also confirmed, even more impressively than the report by Weiller et al., [1998], that GAD is a) the most frequent anxiety disorder seen in primary care (more than 50% of all anxiety disorders), b) rarely correctly diagnosed (only 28% were correctly diagnosed as having GAD by their GP), and c) rarely appropriately managed in terms of type and duration of pharmacological and non-pharmacological treatments [Wittchen et al., 2001].

These findings of increased prevalence of GAD in primary care compared to the general population are in contrast to most other anxiety disorders where the prevalence rate in the general population is much higher than in primary care. This suggests, in line with previous speculations [Schonfeld et al., 1997] that GAD patients are high utilizers of primary care resources (Fig. 1).

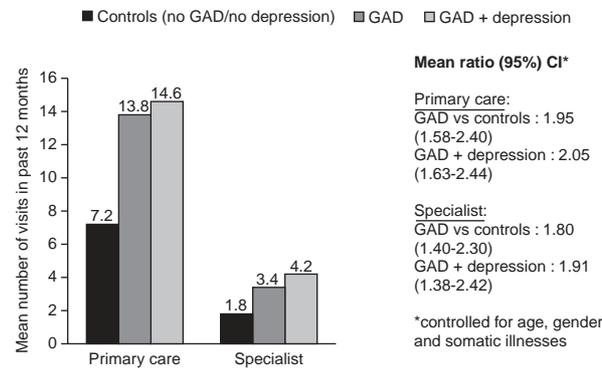


Figure 1. Increased utilization rates of primary care attenders with GAD ($n=14,532$) [Wittchen et al., 2001].

COMORBIDITY

A consistent finding in clinical and epidemiological studies of GAD is the high proportion of comorbidity (Table 2), with common comorbid diagnoses including major depression, panic disorder, social and specific phobia, and post-traumatic stress disorder (PTSD). However, there is no remarkable association with substance use disorders. As many as 66% of patients with current GAD have an additional concurrent psychiatric diagnosis and they almost invariably (90%) have a lifetime history of another psychiatric diagnosis [Wittchen et al., 1994]. The GHS confirmed these findings and reported that comorbidity of DSM-IV GAD includes other anxiety disorders in 55% of cases and depression in 59% of cases [Carter et al., 2001]. Brawman-Mintzer and colleagues [1993] pointed out in this respect that 42% of patients with GAD had experienced at least one major depressive episode during their lifetime. Data from the GHS showed a similar pattern; 40.5% of GAD patients had comorbid current major depression, 59% had comorbid 12-month major depression, and 60% had comorbid lifetime major depression [Carter et al., 2001].

TABLE 2. Comorbidity of current and lifetime DSM-III-R-GAD [Noyes, 2001]

Comorbid disorder	Current GAD (%)	Lifetime GAD (%)
Mania	12.1	10.5
Major depression	38.6	62.4
Dysthymia	22.1	39.5
Panic disorder	22.6	23.5
Agoraphobia	26.7	25.7
Simple phobia	24.5	35.1
Social phobia	23.2	34.4
Alcohol	11.2	37.6
Drug	5.1	27.6
Any of the above	66.3	90.4

GAD, generalized anxiety disorder.

TABLE 3. Proportion of NCS and DSM-III-R disorders with lifetime comorbidity and proportion of temporally primary cases[†]

Disorder	Proportion with lifetime comorbidity (%)	Proportion of temporally primary disorders (%)
Mood disorders		
Mania	99.4	20.2
Dysthymia	91.3	37.7
Major depressive episode	83.1	41.1
Any mood disorder	82.2	—
Anxiety disorders		
Panic disorder	92.2	23.3
Generalized anxiety disorder	91.3	37.0
Agoraphobia	87.3	45.2
Simple phobia	83.4	67.6
Social phobia	81.0	63.1
Post-traumatic stress disorder	81.0	52.1
Any anxiety disorder	74.1	—

[†]Adapted from Kessler RC. 1997. The prevalence of psychiatric comorbidity. In: Wetzler S, Sanderson WC, editors. Treatment strategies for patients with psychiatric comorbidity. New York: John Wiley & Sons. Reproduced by permission of the publisher.

Even slightly higher comorbidity rates have been reported for clinical samples [Noyes, 2001; Roy-Byrne and Katon, 1997]. Although these high rates of anxiety-mood disorder comorbidity have stimulated some controversy over whether GAD should be regarded as a distinct disorder or should more appropriately be conceptualized as a prodromal, residual stage or as a severity marker of depression, there has been little supporting evidence for the latter. Kessler et al. [2001a] have reviewed the available evidence for this controversy and come to the conclusion that GAD and depression are distinct disorders based on the following findings: 1) twin studies do not support the lumping of both conditions, 2) exceedingly high comorbidity rates are confined to selected clinical studies with potential patients' self-selection bias that have used early definition of GAD and not DSM-IV position, 3) conditional rates of comorbidity among GAD cases are not higher

than those observed for other disorders, and 4) there is an abundance of studies revealing that pure and comorbid presentations differ considerably with regard to their clinical and other correlates (Table 3). For example, 50% of all adult GAD cases were found to be temporally primary to mood disorders [Fava et al., 2000; Wittchen et al., 2000]. Comorbidity, especially with depression, significantly lowers the probability of GAD being successfully diagnosed and treated and patients experience more severe symptoms. Comorbid, as opposed to pure, GAD is associated with increased disability and dysfunction, and has a worse prognosis and impairment [Bakish, 1999; Wittchen et al., 2000]. Thus, there is considerable evidence that GAD is a distinct disorder that deserves special research and clinical attention. There is also a need for further studies that provide a better and fuller understanding of the pathogenic and clinical management implications of these patterns of comorbidity.

INDIVIDUAL BURDEN OF DISABILITY

Another key finding that provides further evidence for GAD being a particularly clinically significant mental disorder in itself was the recent demonstration that GAD is associated with a significant burden of disability for individuals, even if they do not have a comorbid condition. This is most notable in terms of diminished functioning both socially and at work. General population studies have considered the degree of impairment caused by pure GAD. The NCS and Midlife Development in the United States Survey both reported that the level of impairment associated with DSM-III-R GAD is substantial and comparable to that of pure major depression [Table 4; Kessler et al., 2001a, 1994, 1997].

A combined analysis of data from these two studies confirmed their findings and showed that even "pure" GAD was associated with marked impairment in role functioning and social life [Kessler et al., 1999]. Moreover, this impairment was equivalent to that caused by major depression (Fig. 2). The highest levels of impairment were seen when GAD was comorbid with major depression (Figure 3).

TABLE 4. Odds ratios of 12-month GAD with major depression without GAD in predicting impairment[†]

Impairment	GAD without MD		MD without GAD		Risk of GAD alone relative to MD alone	
	NCS	MDUSS	NCS	MDUSS	NCS	MDUSS
Fair or poor perceived mental health	6.0*	4.8*	3.3*	5.2*	1.6	0.8
High level of work impairment	3.5	3.5	3.5*	8.5*	0.9	0.5
High level of social impairment	2.5*	1.2	2.0*	1.6*	1.5	1.0

[†]Adapted from Kessler RC, DuPont RL, Berglund P, Wittchen H-U. 1999. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. Am J Psychiatry 156: 1915-1923. Reprinted by permission of the publisher.

*Significant at the 0.05 level, two-sided test

NCS, National Comorbidity Survey [Kessler et al., 1994]; MDUSS, Midlife Development in the United States Survey [Kessler et al., 1999]; GAD, generalized anxiety disorder; MD, major depression.

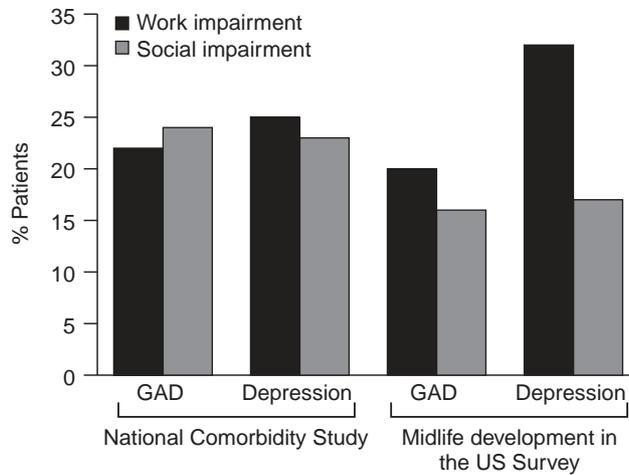


Figure 2. Work and social impairment in GAD and depression [Kessler et al., 1999].

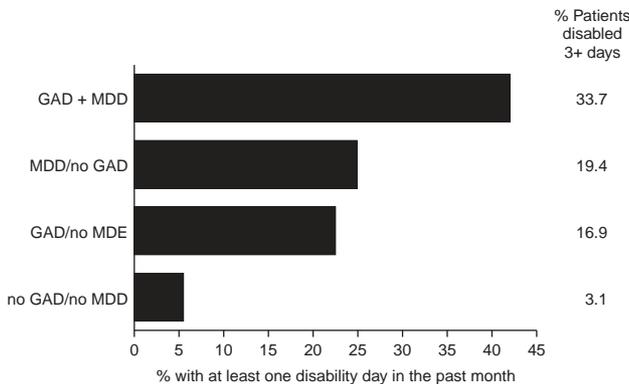


Figure 3. Impairment associated with DSM-III-R GAD [Kessler et al., 1999].

Similar findings were recently reported for DSM-IV GAD from the GHS [Wittchen et al., 2000], which also confirmed similar findings with regard to work productivity as well as other measures of impairment and quality of life [Figure 4; Wittchen et al., 2000].

In the PPGHC study, patients with GAD (and subthreshold GAD) showed greater severity of symptoms and had a greater degree of disability than primary care subjects with no current psychiatric symptoms [Weiller et al., 1998]. Twenty-seven percent of all GAD sufferers reported moderate or severe social disability (assessed by the Brief Disability Questionnaire) and this proportion rose to 59% when GAD was comorbid with major depression.

COST TO SOCIETY

While the level of social disability associated with GAD is as severe as that seen with chronic somatic diseases [Kessler et al., 2001a; Maier et al., 2000], GAD

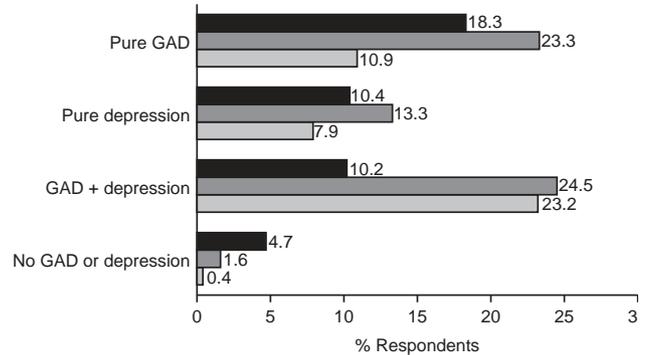


Figure 4. Overall work productivity reductions in pure and comorbid 12-month GAD [Wittchen et al., 2000]. Black bars, 0–10%; gray bars, 11–49%; light gray bars ≥50%.

also has a major impact on society in terms of decreased work productivity and increased health care utilization.

Impact on work productivity. GAD is associated with a significant economic burden owing to particularly decreased work productivity [Kessler et al., 1999; Greenberg et al., 1999; Sou tre et al., 1994; Judd et al., 1998]. A recent analysis using data from the GHS study (see above) considered disability in terms of reduced work productivity in individuals with pure GAD and GAD comorbid with major depression [Wittchen et al., 2000]. Approximately 34% of patients with 12-month pure GAD, 21% of those with depression, and 48% of those with comorbid GAD and depression showed a reduction in work productivity of 10% or more and a reduction of at least 50% in activity during the past month was reported by approximately 11% of respondents with pure GAD and 8% of those with pure major depression (Fig. 4). Thus, GAD is associated with considerable impairment even when no comorbid depression is present. Of those individuals with comorbid GAD and depression, 23% had experienced reductions of at least 50% in the activities of the previous month. In the PPGHC study, the mean number of workdays lost to disability was 4.6 for pure GAD and rose to 8.0 when GAD was comorbid with major depression [Weiller et al., 1998].

Further evidence has been presented by an Australian study, which reported that the burden of mental disorders was third after the burden of heart disease and cancer and, of these mental disorders, the two most relevant were GAD and depression [Andrews et al., 2000]. This was confirmed by Kessler et al. [2001b; Table 5].

This indicates that the presence of GAD is a significant factor that leads to complete disability, diminished productivity at work and that the burden of GAD on society is at least equivalent to, if not greater than, the burden caused by depression.

Health care utilization. The high prevalence of GAD in the primary care setting, compared with the general population, suggests that patients with the disorder are likely to be high users of health care

TABLE 5. Prevalence of 30-day work impairment for selected conditions in the Midlife Development in the United States Survey [Kessler et al., 2001b][†]

Condition	Prevalence of condition (%)	Any work impairment days (%)	Mean number of impairment days	Average per capita number of work impairment days
Physical conditions				
Arthritis	19.4	38.8	8.3	3.2
Hypertension	18.2	34.6	9.0	3.1
Asthma	12.6	44.7	7.7	3.5
Diabetes	5.6	40.2	7.6	3.1
Ulcer	4.4	52.7	10.9	5.8
Mental/substance disorders				
Major depression	14.1	51.9	8.3	4.3
Panic attacks	6.8	56.4	9.5	5.3
Alcohol dependence	4.3	37.1	4.3	1.6
Generalized anxiety disorder	3.3	61.3	9.8	6.0
Drug dependence	2.0	60.8	8.1	4.9

[†]From Kessler RC, Mickelson KC, Barber C. 2001. The effects of chronic medical conditions on work impairment. In: Rossi AS, editor. *Caring and doing for others: social responsibility in the domains of the family, work and community* (John D. and Catherine T. MacArthur Foundation series.). Chicago: University of Chicago Press. Reproduced by permission of the publisher.

services and particularly primary care health services [Maier et al., 2000; Weiller et al., 1998]. According to the most recent primary care study [Wittchen et al., 2002], patients with pure GAD reported a two-fold higher than average number of visits to primary care doctors compared with depressed patients and significantly more visits to non-mental health specialists in the previous 12 months, even when controlling for the presence of physical illnesses. Similarly, GAD ranks third among anxiety disorders (after PTSD and panic disorder) in the rate of use of primary care physicians' time [Kessler et al., 1999]. Approximately one third of patients with GAD seek medical help for their somatic GAD symptoms [Judd et al., 1998], most commonly from primary care physicians. Comorbidity with GAD is reported to increase the rate of help-seeking behavior by more than 50% [Bland et al., 1997].

It has been reported that the specialists seen most often by GAD patients are gastroenterologists [23%; Kennedy and Schwab, 1997]. This was significantly greater than for patients with other anxiety disorders (16% panic disorder, 3% obsessive compulsive disorder; $P < .05$). Only 10% of patients with GAD had seen a psychiatric specialist. These observations were attributed to the considerable overlap between the anxiety symptoms of GAD and the symptoms associated with other conditions, for example, irritable bowel syndrome [Kennedy and Schwab, 1997]. Fifty percent of patients with GAD had seen 1–2 medical specialists (other than primary care physicians) in the preceding year, while 10% had visited 3–5 specialists [Kennedy and Schwab, 1997]. These results show that many patients with GAD visit a number of physicians before they are definitively diagnosed and treated.

It is noteworthy that, despite the high primary care utilization rates of GAD, sufferers are rarely specifi-

cally diagnosed and treated for their disorder either directly by the primary care doctor or after referral to mental health specialists. In the NCS conducted in the early 1990s, only 48% of all pure GAD subjects had received health care intervention at some point in their life, and only 25% had at some point taken medication for their GAD symptoms. The recent GAD-P study (conducted during the year 2000) confirmed this finding and revealed that despite high utilization rates in primary care, less than 10% of GAD patients receive adequate non-pharmacological or pharmacological treatments for their disorder [Wittchen et al., 2001].

Economic burden. The economic cost of anxiety disorders has been examined [DuPont et al., 1996; Greenberg et al., 1999; Rice and Miller, 1998] in elaborate and complex secondary data analyses. These studies indicated that the annual cost of anxiety disorders was \$42–47 billion in the USA in 1990. The three largest components of the total cost comprised \$23 billion (54%) in non-psychiatric medical treatment, \$13 billion (31%) in psychiatric treatment, and over \$4 billion (10%) in indirect workplace costs. Prescription pharmaceutical costs were a minor factor, accounting for less than \$1 billion (2%) of the total cost of anxiety disorders [Greenberg et al., 1999].

The \$4 billion indirect workplace costs reflect an average annual (1990) cost in the workplace of \$256 per affected worker [Greenberg et al., 1999]. A total of 88% of this cost per individual was attributed to lost productivity while at work, as opposed to actual absence from work. Therefore, work productivity may provide a more accurate assessment of the economic cost of GAD than absence from work [Greenberg et al., 1999].

Primary care patients with DSM-III-R anxiety or depressive disorders have been reported to have

markedly higher associated costs (\$2,390/patient) than patients with subthreshold disorders (\$1,098/patient) or those with no anxiety or depressive disorder (\$1397/patient) [Simon et al., 1995]. These cost differences reflected greater utilization of general medical services rather than higher treatment costs.

It is to be expected that the high prevalence of GAD comorbid with depression would lead to increased economic costs. An evaluation of the direct and indirect health care costs in GAD patients found that over 60% were experiencing one or more symptoms of comorbidity that resulted in a high rate of health care utilization that was affected by both the level of comorbidity and symptom severity [Sou tre et al., 1994]. In GAD patients, hospitalizations were significantly more prevalent in those with comorbidity than in those without (11.8% vs. 5.1%, respectively; $P < .001$), with internal medicine and emergency admission being the most frequently used services [Sou tre et al., 1994]. Hospitalization costs accounted for 35% of total costs and over 53% of direct health care costs in patients with comorbidities. The economic cost was also increased in GAD patients with comorbidity in terms of increased absenteeism from work (33.6% with comorbidity vs. 26.6% without; $P < .05$). Absenteeism from work accounted for 34.4% and 33.1% of total costs for patients with and without comorbidity, respectively.

REDUCING THE BURDEN

The debate that existed concerning the status of GAD as a discrete anxiety disorder has meant that less attention has been focused on identification of adequate treatment for the disorder than for other anxiety disorders. Improving the recognition and treatment of GAD is key to reducing the burden of the disorder on the individual and society. The challenges of GAD as a chronic, and after several years, usually complex disorder with a substantial degree of impairment, disability, and comorbid complications are a) its early recognition before substantial complications develop and b) appropriate combined acute and long-term management strategies to reduce the suffering caused by the GAD symptoms and comorbid presentations as well as reducing the associated disability as a major source of relapse. Thus therapeutic interventions should aim at reducing the core symptoms of GAD, the prevalence of comorbidity, and the associated disabilities.

In addition to several well-established, effective non-pharmacological, mostly cognitive-behavioral treatments, there are various traditional drug treatments, most of which have significant limitations, as well as several new drug therapies of first choice.

Benzodiazepines have traditionally been used to treat acute anxiety disorders but they are not ideal for the treatment of chronic GAD. Following long-term therapy, benzodiazepines have the potential to produce

dependency and withdrawal symptoms [Lydiard et al., 1997]. Initial findings in patients with GAD generally showed that buspirone was as efficacious as the benzodiazepines in treating anxiety disorders [Petra ca et al., 1990; Strand et al., 1990] but appeared to lack the side effects and withdrawal symptoms [Laakman et al., 1998]. Although buspirone is effective in most (but not all) studies of GAD [Davidson et al., 1999; Lydiard, 2000], its lack of efficacy against comorbid conditions is the main reason for it not being recommended as a first-line treatment for GAD [Ballenger et al., 2001].

The use of buspirone for the treatment of anxiety disorders is limited to short-term treatment only and therefore is inadequate for the treatment of GAD. In a placebo-controlled study to investigate the use of both buspirone and hydroxyzine in patients with GAD, a significant difference was shown only between hydroxyzine and placebo with respect to improvement of the primary efficacy measurement (improvement on the Hamilton Anxiety Scale). However, both buspirone and hydroxyzine were shown to be more effective than placebo for the secondary efficacy measurement (improvement in CGI and HAD scale ratings) [Lader and Scotto, 1998]. Treatment with benzodiazepines or buspirone is ineffective when comorbid depression is present [Bakish, 1999; Lydiard et al., 1987].

There is evidence that the tricyclic antidepressants (TCAs) are at least as effective as benzodiazepines in the treatment of GAD and may be superior in long-term therapy [Kahn et al., 1986; Hoehn-Saric et al., 1988; Rickels et al., 1993]. The tertiary TCAs, which have dual serotonergic-noradrenergic effects (e.g., imipramine and amitriptyline), appear to be consistently effective in the treatment of anxiety [Feighner, 1999]. However, side effects, such as anticholinergic events, preclude the use of TCAs in many patients, namely, the elderly or those with cardiovascular disease.

Clinical studies have shown that the selective serotonin reuptake inhibitor (SSRI) paroxetine and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine are as effective in the treatment of GAD as they are for most other anxiety disorders studied so far [Bellew et al., 2001; Davidson et al., 1999; Davidson, 2001; Feighner, 1999; Gelenberg et al., 2000; Pollack et al., 2001; Rocca et al., 1997], resulting in a reduction of the symptoms of anxiety and depression. An important advantage of these drugs is that it is useful in the treatment of the depression and anxiety disorders frequently comorbid with GAD, such as panic disorder, social anxiety disorder, or OCD [Ballenger et al., 2001]. Paroxetine, which has proven efficacy across the spectrum of depression and anxiety disorders (panic disorder [Lecrubier et al., 1997], OCD [Zohar and Judge, 1996], social anxiety disorder [Lydiard and Bobes, 2000], and PTSD [Beebe et al., 2000]), has also been shown to be effective in patients with GAD [Bellew et al., 2000; Pollack et al., 2001; Rocca et al., 1997] and has been the first SSRI to be

specifically licensed for the treatment of GAD. A large clinical program involving 1,264 patients in three 8-week studies has shown that paroxetine significantly reduces HAM-A total scores compared with placebo and reduces the core GAD symptoms (worry, anxiety, and tension). Paroxetine treatment results in a significant improvement in quality of life in GAD [Pollack et al., 2001]. The EuroQol visual analogue scale (EQ-5D VAS) provides a measure of quality of life by assessing general well-being and the mean change from baseline in EQ-5D VAS scores was significantly greater with paroxetine than with placebo [Bellew et al., 2000].

Controlled studies have also demonstrated that the SNRI, venlafaxine extended release (XR) (which is also licensed for GAD) are effective in both the short- and long-term treatment of GAD [Allgulander et al., 2001; Davidson et al., 1999; Gelenberg et al., 2000; Rickels et al., 2000; Silverstone and Salinas, 2001].

In the first of these studies, the mean adjusted HAM-A anxious mood and tension scores were significantly lower for both doses of venlafaxine XR at week 8 compared with placebo [$P < .05$; Davidson et al., 1999]. However, the adjusted mean total HAM-A scores for all the treatment groups compared to placebo were not significantly different.

In the study by Rickels et al. [2000], venlafaxine XR 75, 150, and 225 mg/day over 8 weeks were significantly more effective than placebo in the treatment of GAD in 377 outpatients without major depressive disorder.

The study by Gelenberg et al. [2000] evaluated flexible doses of venlafaxine XR over 6 months. The results showed that the efficacy of venlafaxine XR 75–225 mg/day could be sustained in 238 patients with GAD over a 28-week maintenance period. Similarly, in the 24-week placebo-controlled study by Allgulander et al. [2001], venlafaxine XR 37.5, 75, and 150 mg/day were significantly more effective than placebo in the treatment of GAD in 541 outpatients.

The placebo-controlled study by Silverstone and Salinas [2001] compared the efficacy of venlafaxine XR (75–225 mg) over 12 weeks in patients with major depression and patients with comorbid GAD. In the comorbid patients, venlafaxine significantly decreased both HAM-D and HAM-A scores compared with placebo.

The rapidly increasing evidence that SSRIs and SNRIs are highly effective treatments for GAD and are also equally effective in the treatment of major depression and the other anxiety disorders (which frequently comorbid with GAD) suggests that these strategies are the drug treatments of first choice for current practice. They also have the potential greatly to reduce the individual and economic burden of GAD.

CONCLUSIONS

GAD is a recognizable and distinct anxiety disorder that is associated with a significant burden of disability on the individual, the magnitude of which is at least

equivalent to that of major depression [Kessler et al., 1999; Wittchen et al., 2001]. However, a comprehensive and sound estimation of the burden of GAD on the individual and society is complicated by the high prevalence of comorbid disorders. Patients with comorbid GAD and depression are particularly likely to demonstrate disability and dysfunction. The presence of GAD in other somatic and mental disorders seems to magnify the disability found for the other condition per se. Further investigations into the associated burden of GAD as well as a change in the current approach to the recognition and treatment of the disorder are necessary.

GAD reduces work productivity and increases the utilization of health care services [Greenberg et al., 1999; Souëtre et al., 1994], and comorbidity, particularly with depression, further increases levels of impairment and cost [Bakish, 1999; Greenberg et al., 1999; Souëtre et al., 1994; Weiller et al., 1998]. In addition, patients with GAD who present to medical practitioners with somatic symptoms may not be diagnosed as suffering from a psychiatric condition, leading to increased medical utilization until the true condition is revealed [Lydiard, 2000].

Although there is growing emphasis on the identification of new agents for the treatment of GAD, further research on the response of comorbidity to management is crucial. Of the current drug treatment options, the SSRI paroxetine and the SNRI venlafaxine are the most convenient treatment to use in the primary care setting and is specifically licensed for the treatment of GAD (DSM-IV definition). Both agents have proven efficacy across the spectrum of depressive and anxiety disorders that are frequently comorbid with GAD (panic disorder, social anxiety disorder, obsessive-compulsive disorder, and PTSD; Brawman-Mintzer et al., 1993; Ballenger et al., 2001; Davidson, 2000).

Prompt recognition and effective treatment of GAD are central to reducing the burden of this chronic, prevalent, and disabling condition. Greater availability of effective outpatient treatment for GAD will improve symptoms and functionality, reduce disability and health care utilization, and could substantially reduce the economic and social burden of this common and disabling disorder.

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State of New Jersey
DEPARTMENT OF HEALTH
PO BOX 360
TRENTON, N.J. 08625-0360

PHILIP D. MURPHY
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Lt. Governor

SHEREEF M. ELNAHAL, MD, MBA
Acting Commissioner

March 22, 2018

Re: Final Agency Decision: Petitions to Establish Additional
Debilitating Medical Conditions under the New Jersey Medicinal
Marijuana Program

Dear Petitioners:

This letter sets forth the basis, rationale and final decision in the matter of the Department of Health's (Department) Request for Petitions to establish additional debilitating medical conditions under the New Jersey Medicinal Marijuana Program (MMP). As explained in detail below, I am granting the petitions seeking to add chronic pain conditions that are related to musculoskeletal disorders, chronic pain conditions that are of a visceral origin, as well as Tourette's Syndrome, migraine, and anxiety as debilitating medical conditions under the MMP. However, I am denying the petitions seeking to add asthma and chronic fatigue syndrome to the MMP.

In reaching this decision, I considered the Request for Petitions, the petitions submitted in response to the Request, the MMP panel's recommendations, written and oral public comments received regarding various petitions, as well as the requirements of the New Jersey Compassionate Use Medical Marijuana Act (the Act), N.J.S.A. 24:6I-1 et seq., and the regulations promulgated thereunder. The referenced materials are incorporated herein and made a part of this final decision.

The Request for Petitions

On July 5, 2016, the Department published the Request for Petitions in the New Jersey Register advising that from August 1, 2016 to August 31, 2016, it was accepting petitions to establish additional medical conditions as "debilitating" under the MMP. 48 N.J.R. 1395(a). The Request for Petitions stated that the Department was seeking petitions in accordance with the Act, which authorizes the Department to include additional debilitating medical conditions under the MMP.

In the Request for Petitions, the public was advised that submitted petitions were required to include the following information, pursuant to N.J.A.C. 8:64-5.3:

- (1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;

(2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;

(3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting, or otherwise severely impair the patient's ability to carry on activities of daily living;

(4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;

(5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and

(6) Letters of support from physicians or other licensed health care professional knowledgeable about the condition.

The Department also crafted a Petition Form that petitioners could use for their submissions. The form detailed the above-listed criteria, which each petitioner needed to provide in order for his or her submission to be accepted and considered.

In addition to publishing the request for petitions in the New Jersey Register, the Department also posted it on its website.

Completeness Review

At the close of the petition submission period, the Department received sixty-eight petitions. Thereafter, the Department reviewed each petition to determine whether it contained the information that was required for it to be accepted for consideration. From its review, the Department determined that twenty-three petitions did not meet the criteria for consideration.¹ Accordingly, the Department denied these petitions under separate cover on December 7, 2016, pursuant to N.J.A.C. 8:64-5.3(b). The remaining forty-five petitions met the criteria for consideration and were accepted.

Statutory and Regulatory Criteria

The Act charges the Department with the responsibility of administering the State's MMP, including establishing a registry of qualifying patients and primary care givers. To qualify as a MMP patient, an individual must suffer from one of the debilitating medical conditions set forth in the Act. The Act defines a "debilitating medical condition" as:

(1) one of the following conditions, if resistant to conventional medical therapy: seizure disorder, including epilepsy; intractable skeletal muscular spasticity; post-traumatic stress disorder; or glaucoma;

¹ Legislation was enacted during the pendency of the petitions, which added post-traumatic stress disorder to the list of conditions that qualify as debilitating under the MMP. As a result, the petitions seeking to add this condition to the MMP were deemed moot and not forwarded to the Panel for consideration.

(2) one of the following conditions, if severe or chronic pain, severe nausea or vomiting, cachexia, or wasting syndrome results from the condition or treatment thereof: positive status for human immunodeficiency virus; acquired immune deficiency syndrome; or cancer;

(3) amyotrophic lateral sclerosis, multiple sclerosis, terminal cancer, muscular dystrophy, or inflammatory bowel disease, including Crohn's disease; [or]

(4) terminal illness, if the physician has determined a prognosis of less than 12 months of life.

[N.J.S.A. 24:6I-3.]

In addition to the conditions listed in the Act, the Legislature authorized the Department to establish additional medical conditions as debilitating under the MMP. Ibid. Consistent with its statutory authority, the Department promulgated rules that outline the process for expanding the list of medical conditions that qualify as "debilitating" under the MMP. See N.J.A.C. 8:64-1.1 et seq. Pursuant to these rules, I am required to take into consideration the following factors in order to determine whether a condition should be added to the MMP as a "debilitating" medical condition that is likely to benefit from the use of medical marijuana to treat or alleviate the debilitating effect of the condition:

(1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;

(2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;

(3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living;

(4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;

(5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and

(6) Letters of support from physicians or other licensed health care professionals knowledgeable about the condition.

[N.J.A.C. 8:64-5.3]

The MMP Review Panel Meetings, Public Comments and Panel Recommendations

On May 11, 2017, the MMP Review Panel, which is a panel assembled by the Department to review and make recommendations on petitions seeking to add conditions to the MMP, met to

review and hear public comments on the forty-five accepted petitions. At the meeting, the Panel acknowledged that they reviewed the material submitted with the petitions and that they also conducted their own independent analysis and research for each condition. During the meeting, the Panel also advised that it grouped the petitioned conditions into seven categories, namely chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, anxiety, asthma and chronic fatigue. After offering a panel discussion on each condition and hearing public comments from two individuals, both of whom expressed support for the MMP, the Panel voted on each petition. Based upon a majority vote of the members who were present at the meeting, the Panel recommended that chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety be approved as debilitating conditions under the MMP and recommended denial of asthma and chronic fatigue.

After the meeting, the Chairman of the Panel reduced the Panel's initial recommendations to writing and submitted it to the Department's Commissioner for consideration. In the initial recommendation letter, the Panel advised that it was recommending that the Commissioner add chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety to the MMP because these conditions are debilitating and medicinal marijuana was more likely than not to have the potential to be beneficial to treat or alleviate the debilitation associated with each condition.

As for asthma and chronic fatigue, the Panel recommended that these conditions not be added to the MMP because medical marijuana was not likely to have the potential to be beneficial to treat or alleviate the debilitation associated with the conditions.

After receiving the Panel's initial recommendation letter, it was posted on the Department's website for a 60-day public comment period to provide the public with an opportunity to submit written comments on the recommendations. At the time the comment period closed, the Department received approximately sixty comments, which were generally supportive of the MMP.

During the 60-day comment period, the Department's MMP Review Panel also convened a public hearing on September 18, 2017, which provided the public with an additional opportunity to comment on the recommendations. During this public hearing, the Panel heard from seven individuals. The comments provided by the commenters did not express any disagreement with the Panel's recommendations.

Upon the conclusion of the public comment period, the Panel reconvened for a final meeting on the petitions. At the meeting, which was held on October 26, 2017, the Panel further deliberated its recommendations on the petitioned conditions, taking into consideration the petitions, information submitted with the petitions, public comments, the factors outlined in N.J.A.C. 8:64-5.3, each member's own research or that done by others, as well as each member's education and training, in order to determine whether any changes should be made to the Panel's initial recommendations. In so deliberating, the Panel discussed each condition in turn and permitted additional public comment on the conditions. Based upon the Panel's extensive and thorough discussions, the majority of the Panel members present at the meeting voted to uphold their initial recommendations on the conditions. As such, the Panel's initial recommendations converted to the Panel's final recommendations to the Commissioner, pursuant to N.J.A.C. 8:64-5.3(f).

Findings and Decisions on the Petitions

For the reasons that follow, I am granting the petitions seeking to add chronic pain that is related to musculoskeletal disorders, chronic pain conditions that are of a visceral origin, as well as Tourette's Syndrome, migraine, and anxiety as debilitating medical conditions under the MMP and denying the petitions seeking to include asthma and chronic fatigue syndrome under the MMP. My decision is consistent with the Panel's recommendations. In reaching my decision, I considered the statutory and regulatory criteria articulated above, the Panel's recommendations and their supporting materials, the petitions with supporting information, public comments and the transcripts of the Panel's meetings, which provides the Panel members' detailed discussions on each condition.

Granted Petitions

Chronic Pain associated with a Musculoskeletal Disorder

Based upon my independent review of the petitions, I am granting those seeking to add chronic pain associated with a musculoskeletal disorder to the MMP.² In coming to this conclusion, I reviewed this condition against the six regulatory criteria cited above and found that it meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic pain associated with a musculoskeletal disorder is a valid condition. According to the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), chronic pain associated with a musculoskeletal disorder is pain that persists beyond the usual course of an acute condition, which is typically three months or more or past the time for normal healing, and includes injury and inflammatory conditions "that cause pain in the body's joints; ligaments; muscles; nerves; tendons; and structures that support the limbs, neck, and back."³ Moreover, as noted by the Panel, the World Health Organization's International Classification of Diseases, as clinically modified by the NCHS (ICD-10-CM), uses unique alphanumeric codes to identify known diseases and other health problems and lists multiple codes for chronic pain.⁴ Given the fact that chronic pain associated with a musculoskeletal disorder has a common medical definition and maintains several ICD-10-CM codes, which entities covered by the Health Insurance Portability and Accountability Act must use for processing claims pursuant to rules promulgated by the U.S. Department of Health and Human Services, I find that chronic pain associated with a musculoskeletal disorder is a valid condition recognized by the medical community. See 45 C.F.R. 162.

² Thirty-five of the petitions received by the Department concern various forms of chronic pain. After reviewing these petitions, the Panel determined that they fell into two categories: chronic pain associated with a musculoskeletal disorder and chronic pain of a visceral origin. Based upon my review of this matter, I find that the Panel made the appropriate categorizations of these petitions. Thus, I agree with the Panel that the chronic pain conditions sought to be added to the MMP should be generally labeled as chronic pain associated with a musculoskeletal disorder and chronic pain of a visceral origin, rather than the unique, individual conditions set forth in each chronic pain petition. The list of petitions that fall into each category are set forth in the Panel's recommendation letter, which is incorporated herein by reference.

³See <https://www.cdc.gov/nchs/data/nhsr/nhsr098.pdf> (last visited March 13, 2018). See also <https://www.cdc.gov/drugoverdose/prescribing/guideline.html> (last visited March 13, 2018).

⁴ See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited March 13, 2018).

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. As set forth in the petitions and acknowledged by the Panel, the generally accepted treatments for chronic pain associated with a musculoskeletal disorder are opioids and non-steroid anti-inflammatory drugs (NSAIDs), both of which can have significant side effects. I agree. According to the Centers for Disease Control and Prevention (CDC), NSAIDs, such as ibuprofen, are a common treatment for chronic pain associated with a musculoskeletal disorder.⁵ The CDC also recognizes opioids, such as oxycodone and hydrocodone, as a common and medically accepted treatment for chronic musculoskeletal pain.⁶ Thus, I find that the treatments for chronic pain, namely NSAIDs and opioids, are recognized and accepted by the medical community and relate to a patient's suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that chronic pain associated with a musculoskeletal disorder itself as well as the treatment for this condition cause severe suffering for patients inflicted with this condition. As the name suggests, a patient with chronic pain associated with a musculoskeletal disorder experiences just that - pain. Specifically, musculoskeletal chronic pain can cause widespread or localized pain that may worsen with movement, stiffness or achiness, fatigue, and/or muscle twitches.⁷ Thus, the condition itself is the main culprit for the suffering experienced by patients with this disorder. While chronic pain, in and of itself, causes extensive pain, the treatment for chronic pain associated with a musculoskeletal disorder can also cause significant suffering. Specifically, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness⁸. And, opioids can cause constipation, nausea, respiratory depression, dependency, sedation and dizziness.⁹ All of these side effects can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that musculoskeletal chronic pain as well as the therapies to treat this condition cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatments for chronic musculoskeletal pain that cause the patient suffering, namely NSAIDs and opioids, are essentially the most viable conventional medical therapies offered for this condition, which was noted by the Panel. As such, I find that there is an absence of effective alternative medical therapies to the conventional therapies currently prescribed for chronic musculoskeletal pain that cause patients to suffer.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is extensive research establishing that the use of medical

⁵ See https://www.cdc.gov/drugoverdose/pdf/nonopioid_treatments-a.pdf (last visited March 13, 2018).

⁶ See <https://www.cdc.gov/drugoverdose/opioids/index.html> (last visited March 13, 2018).

⁷ See <https://my.clevelandclinic.org/health/diseases/14526-musculoskeletal-pain> (last visited March 13, 2018).

⁸ See <https://my.clevelandclinic.org/health/drugs/11086-non-steroidal-anti-inflammatory-medicines-nsaids> (last visited March 13, 2018).

⁹ See Footnote 6.

cannabis can relieve the chronic pain associated with a musculoskeletal disorder. Specifically, there are several peer-reviewed publications in leading medical journals, including a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, as well as a significant number of clinical trials, which found that the use of medical marijuana was effective in relieving chronic pain.¹⁰ As such, I find that there is general acceptance in the medical community that medicinal cannabis can alleviate the suffering caused by chronic musculoskeletal pain.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic musculoskeletal pain under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of chronic pain related to a musculoskeletal disorder is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that chronic pain related to a musculoskeletal disorder should be added to the MMP.

Chronic Pain Conditions of a Visceral Origin

From my detailed review of the petitions, I am granting those seeking to add chronic pain conditions of a visceral origin to the MMP. In coming to this conclusion, I reviewed the petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

For the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic pain of a visceral origin is a valid condition. Chronic pain of a visceral origin is commonly defined by the medical community as pain that arises from the internal organs of the body and persists beyond the usual course of an acute condition, which is typically three months or more or past the time for normal healing.¹¹ Specifically, visceral pain is pain that results from the activation of nociceptors located in most viscera (internal organs of the body, specifically those within the chest (as the heart or lungs) or abdomen (as the liver, pancreas or intestines)) and the surrounding connective tissue.¹² Moreover, as noted by the Panel, there are multiple ICD-10-CM codes for chronic pain of a visceral origin, such as codes for pancreatitis, pain related to neurogenic bladder and bowel dysfunction, and irritable bowel syndrome. Because there is a common medical definition for chronic visceral pain as well as many ICD-10-CM codes for this condition, I find that chronic pain of a visceral origin is a valid and recognized medical condition.

As for the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community

¹⁰ See, e.g., The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research, National Academies Press (2017) (<http://nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx>) (last visited March 13, 2018); Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials, British Journal of Clinical Pharmacology (2001) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243008/>) (last visited March 13, 2018).

¹¹ See <https://medical-dictionary.thefreedictionary.com/visceral+pain> (last visited March 13, 2018).

¹² See <https://www.merckmanuals.com/professional/neurologic-disorders/pain/overview-of-pain> (last visited March 13, 2018).

and other experts as valid treatments for the condition. Like chronic musculoskeletal pain, chronic pain of a visceral origin is generally treated with opioids and NSAIDs, which, as I stated above, can have severe side effects. Indeed, the CDC advises that NSAIDs and opioids are the most common forms of treatment for chronic pain.¹³ Thus, I find that the treatments for chronic pain, namely NSAIDs and opioids, are recognized and accepted by the medical community as the treatments for chronic visceral pain and relate to a patient's suffering.

Regarding the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the chronic pain condition itself as well as the treatments for this condition cause severe suffering for patients stuck with this disorder. Specifically, visceral pain due to an obstruction of a hollow organ is poorly localized, deep, and cramping and may be referred to remote cutaneous sites.¹⁴ Visceral pain that is caused by an injury of organ capsules or other deep connective tissues may be more localized and sharp.¹⁵ As such, the actual condition is the main cause for the suffering experienced by patients with this disorder. Although chronic pain itself causes severe pain, the treatment for this condition can also result in significant suffering. As I outlined above, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness. And, opioids can cause constipation, nausea, respiratory depression, dependency, sedation and dizziness. So, the condition itself as well as the side effects from the medications used to treat this condition can prevent a patient from engaging in activities of daily living and eviscerate one's quality of life. Accordingly, I find that both the condition of chronic pain as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatments for chronic pain that cause the patient suffering, which are NSAIDs and opioids, are the only viable conventional medical therapies offered for this condition.¹⁶ Therefore, I find that there is a lack of medically-accepted, alternative medical treatments to the conventional therapies currently recommended for chronic pain of this nature.

As for the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, the Panel concluded that there is comprehensive research demonstrating that the use of medicinal cannabis can alleviate the pain associated with chronic pain. As stated above, there are peer-reviewed publications in leading medical journals, including a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, and a number of clinical trials that found that the use of medical marijuana was effective in relieving chronic pain. As such, I find that the medical community has generally accepted the use of medicinal marijuana as a likely effective treatment for alleviating the suffering caused by chronic pain.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic

¹³ See footnotes 5 and 6.

¹⁴ See footnote 12.

¹⁵ Ibid.

¹⁶ Ibid.

visceral pain under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of chronic pain of a visceral origin is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that chronic pain of a visceral origin should be added to the MMP.

Tourette’s Syndrome

After a careful review of the petition seeking to add Tourette’s Syndrome (TS) to the MMP, I have decided to grant this petition. In formulating this determination, I reviewed the condition against the six regulatory criteria cited above and found that it meets the requirements for inclusion in the MMP.

Under the first factor, I must determine whether the condition is generally accepted in the medical community as a valid medical condition. I find that TS meets this requirement. Specifically, TS is commonly defined by the medical community as a neurological disorder characterized by repeated involuntary movements (motor tics) and uncontrollable vocal sounds (vocal tics), with symptoms usually manifesting before the age of eighteen.¹⁷ Moreover, a CDC study found that “1 of every 360 (0.3%) children 6 – 17 years of age in the United States have been diagnosed with TS based on parent[al] report[s],” with boys being “three to five times more likely to have TS than girls.”¹⁸ Accordingly, I find that TS is a valid and recognized medical condition.

Regarding the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient’s suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. According to the petition and as acknowledged by the Panel, the generally accepted treatments for TS are medication and behavioral treatments, which can help manage the tics.¹⁹ As noted by the Panel, there is no one primary medication to treat TS and, as a result, there is a varying approach to how it is addressed.²⁰ Most medications prescribed for TS have not been approved by the U.S. Food and Drug Administration (FDA) for treating tics and the medications that are approved fall into the category of anti-psychotics, which can have serious adverse side effects that include weight gain, stiff muscles, tiredness, restlessness, and social withdrawal.²¹ As such, I find that the treatments for the symptoms of TS are recognized and accepted by the medical community as the treatments for this condition and relate to a patient’s suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient’s ability to carry on activities of daily living, I find that both TS itself as well as co-occurring conditions and the treatments for this condition cause severe

¹⁷ See <http://www.merckmanuals.com/professional/pediatrics/neurologic-disorders-in-children/tic-disorders-and-tourette-syndrome-in-children-and-adolescents> (last visited March 13, 2018).

¹⁸ See <https://www.cdc.gov/ncbddd/tourette/data.html> (last visited March 13, 2018).

¹⁹ See <https://www.cdc.gov/ncbddd/tourette/treatments.html> (last visited March 13, 2018).

²⁰ In Re: Medicinal Marijuana Review Panel Transcript. 55: 4 -6. October 25, 2017.

²¹ See footnote 19.

suffering for patients inflicted with this condition. While the tics caused by TS clearly impair a patient's ability to carry on his or her activities of daily living, the co-occurring conditions that arise with this disorder can be equally if not more devastating to the patient. According to the National Institute of Neurological Disorders and Stroke, many individuals with TS experience additional neurobehavioral problems that often cause more impairment than the tics themselves. These include inattention, hyperactivity and impulsivity (attention deficit hyperactivity disorder — ADHD), problems with reading, writing, and arithmetic, and obsessive-compulsive symptoms such as intrusive thoughts/worries and repetitive behaviors.²² Thus, TS itself along with its co-occurring conditions negatively impact a patient's quality of life. Additionally, as I noted above, the pharmacological treatments for TS can cause serious side effects that negatively impact an individual's quality of life. As recognized by the Panel, TS is difficult to treat and very debilitating.²³ I concur. As such, I find that both the condition of TS as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must analyze the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the only FDA-approved therapies for TS are anti-psychotic medications. While these medications have an 80% rate of tic suppression, which was noted by the Panel, the medications have serious side effects that can include weight gain and social withdraw. And, although behavioral therapy is a treatment that teaches people with TS ways to manage their tics, it is not a cure for tics. As such, the conventional therapies for TS, which are pharmaceutical and behavioral treatment, may not fully suppress or manage tics and the presence of TS may severely impair the patient's ability to carry on activities of daily living. Accordingly, I find that there is a lack of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for TS that cause suffering for some patients.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is research establishing that the use of medical cannabis can relieve the symptoms associated with TS. Evidence on the use of cannabis for effective symptomatic treatment of movement disorders, including TS, dates to the late 1990s with the work of Dr. Kirsten Müller-Vahl of the Hannover Medical School in Hannover, Germany.²⁴ Dr. Müller-Vahl's studies demonstrated improvements in global functioning and tic severity scores with cannabis use. Specifically, Dr. Müller-Vahl conducted a clinical survey among sixty-four TS patients of whom seventeen had reportedly consumed cannabis and approximately 82% of these patients reported a reduction in symptoms.²⁵ Subsequent studies of single cases confirmed that administration of 10mg of tetrahydrocannabinol (THC), which is one of the active chemical compounds in cannabis, led to an 80% reduction in tics and a simultaneous increase in the attention of patients.²⁶ And, a randomized, placebo-controlled six-week trial of up to 10mg THC

²² <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Tourette-Syndrome-Fact-Sheet> (last visited March 13, 2018).

²³ In Re: Medicinal Marijuana Review Panel Transcript. 54:11. October 25, 2017.

²⁴ Müller-Vahl, K R., et al. "Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol." *American Journal of Psychiatry* 156.3 (1999): 495-495 .

²⁵ See <http://researchfeatures.com/2017/06/01/cannabis-based-medication-tourettes-syndrome/> (last visited March 13, 2018).

²⁶ *Ibid.*

per day confirmed the previous findings.²⁷ Furthermore, 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.²⁸ Moreover, several states, such as Minnesota and Illinois, have approved medical marijuana specifically for the treatment of TS. Even more, a recent systematic review and meta-analysis published in the Journal of the American Medical Association (JAMA) in 2015 suggests there is some evidence that cannabinoids may improve symptoms of TS.²⁹ While the 2015 JAMA review suggests that marijuana may only have a minimal effect on relieving the symptoms of TS, the fact that the study evidenced some relief, even with the limited number of clinical trials available on the medical benefits of marijuana due to the legal restrictions surrounding cannabis, shows promise that marijuana is effective for this condition. As such, I find that the totality of the above research exhibits a general consensus in the medical community that marijuana is likely to alleviate some of the suffering caused by TS.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of TS under the MMP, I find that the petition was submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of TS is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that Tourette’s Syndrome should be added to the MMP.

Migraine

After a thorough review of the petitions, I am granting those seeking to add migraine to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that migraine meets this criteria. According to the Merck Manual, migraine is an episodic primary headache disorder.³⁰ Symptoms typically last four to seventy-two hours and may be severe.³¹ Pain is often unilateral, throbbing, worsen with exertion, and accompanied by symptoms such as nausea and sensitivity to light, sound, or odors. Auras occur in about 25% of patients, usually just before but sometimes after the headache.³² And, there are approximately 28 million individuals living with migraines in the United States.³³ As such, I find that migraine is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient’s suffering and the extent to which the treatments

²⁷ ibid.

²⁸ See <https://www.nap.edu/read/24625/chapter/6?term=tourette#104> (last visited March 13, 2018).

²⁹ See <https://media.jamanetwork.com/news-item/mixed-findings-regarding-quality-of-evidence-supporting-benefit-of-medical-marijuana/> (last visited March 13, 2018).

³⁰ See <http://www.merckmanuals.com/professional/neurologic-disorders/headache/migraine> (last visited March 13, 2018).

³¹ ibid.

³² ibid.

³³ <https://www.hopkinsmedicine.org/otolaryngology/docs/Migraine%20patient%20handout.pdf> (last visited March 13, 2018).

causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. As stated in the petitions and recognized by the Panel, the generally accepted treatments for migraines are NSAIDs, triptans, opioids and/or ergots (ergot alkaloids), all of which can have significant side effects.³⁴ Specifically, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness.³⁵ Side effects of triptans include nausea, dizziness, drowsiness and muscle weakness.³⁶ Furthermore, triptans should not be used by those who have a past history of, or risk factors, for heart disease, high blood pressure, high cholesterol, angina, peripheral vascular disease, impaired liver function, stroke or diabetes.³⁷ Ergots may worsen nausea and vomiting related to migraines, and it may also lead to medication-overuse headaches.³⁸ And, as outlined above, opioids have serious side effects including addiction and nausea.³⁹ Thus, I find that the treatments for migraine, namely NSAIDs, triptans, opioids and ergots, can cause a patient to suffer and are accepted by the medical community as the treatments for this condition.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the migraine condition itself as well as the treatments for this condition cause severe suffering for patients. As stated above, the condition itself causes intense pain, nausea and sensitivity to light, sound, or odors. In fact, the pain and sensitivity may become so intense that the patient may have no other option than to rest in a dark, quiet room until the migraine passes.⁴⁰ Thus, the migraine condition causes severe suffering.

The same holds true for migraine treatments. The side effects caused by the treatments for migraines can be equally if not worse than the symptoms produced by this condition. Specifically, the treatments, which include opioids and triptans, can cause nausea, dizziness, and muscle weakness and may even cause rebound symptoms that are more intense than the original onset of the migraine.⁴¹ Thus, the migraine condition as well as side effects accompanying the treatment for this condition impair or even prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. With this, I find not only that the migraine condition in and of itself causes a patient severe suffering but that the therapies to treat it also cause significant suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. The treatments for migraine that cause the patient suffering, namely

³⁴ <https://www.hopkinsmedicine.org/otolaryngology/docs/Migraine%20patient%20handout.pdf> (last visited March 13, 2018). See also <https://www.mayoclinic.org/diseases-conditions/migraine-headache/diagnosis-treatment/drc-20360207> (last visited March 13, 2018).

³⁵ See <https://my.clevelandclinic.org/health/drugs/11086-non-steroidal-anti-inflammatory-medicines-nsaids> (last visited March 13, 2018).

³⁶ See <http://www.headaches.org/2007/10/25/triptans/> (last visited March 13, 2018).

³⁷ *Ibid.*

³⁸ See <https://www.drugs.com/mcd/migraine> (last visited March 13, 2018).

³⁹ See footnote 6.

⁴⁰ <https://www.hopkinsmedicine.org/otolaryngology/docs/Migraine%20patient%20handout.pdf> (last visited March 13, 2018).

⁴¹ *Ibid.*

NSAIDs, triptans, opioids and ergots, are the conventional medical therapies offered for this condition. Furthermore, as noted by the Panel, the conventional therapies are ineffective for some patients, leaving them with a decreased ability to function and a decreased quality of life. Alternatives such as biofeedback, ice packs, acupressure, aromatherapy, adequate sleep, smoking cessation, avoiding any food and environmental triggers are available and may alleviate migraine symptoms.⁴² However, these alternative treatments usually do not treat all of the symptoms associated with a migraine and do not necessarily alleviate the patient's suffering caused by the migraine. Therefore, patients that are not responsive to conventional or alternative therapies may suffer constant unrelenting pain, which produces mental and physical debilitation. As such, I find that there are serious limitations with the medically-accepted, alternative medical therapies and the conventional therapies currently prescribed for migraine.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is extensive research establishing that the use of medical cannabis can relieve the pain associated with migraine. There are studies which found that the use of medical marijuana was effective in decreasing the frequency of migraine headaches and relieving migraine pain.⁴³ Most notably, a recent study recommended that prospective studies should be conducted to explore a cause-and-effect relationship and the use of different strains, formulations, and doses of marijuana to better understand the effects of medical marijuana on migraine headache treatment and prophylaxis.⁴⁴ A majority of the Panel agreed that a review of the literature suggests that marijuana might alleviate some of the symptoms caused by a migraine with less side effects than commonly accepted medical treatment. Based upon this research, I find that there is generally accepted evidence in the medical community that medicinal cannabis can alleviate the suffering caused by migraine.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of migraine under the MMP, I find that the petitions were submitted with support from physicians and an advanced practice nurse. Indeed, one petition was submitted by a board certified anesthesiologist. Thus, I find that this requirement is met.

Based upon the above analysis, I find that the condition of migraine is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that migraine should be added to the MMP.

Anxiety

Based upon my independent review of the petitions, I am granting those seeking to add anxiety to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

⁴² *Ibid.* See also <https://migraine.com/complimentary-and-alternative-therapies/> (last visited March 13, 2018).

⁴³ Ethan B. Russo, Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes, *Cannabis and Cannabinoid Research*, 20a6, 1,1, 154. See <https://www.liebertpub.com/doi/10.1089/can.2016.0009> (last visited March 13, 2018).

⁴⁴ See <https://www.ncbi.nlm.nih.gov/pubmed/26749285> (last visited March 13, 2018).

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that anxiety satisfies this criteria. Specifically, the American Psychiatric Association defines anxiety and anxiety disorders as conditions characterized by excessive fear and behavioral disturbances.⁴⁵ Anxiety results from anticipation of a future threat and may be associated with symptoms of muscle tension, vigilance in preparation for future danger, and overly cautious or avoidant behaviors.⁴⁶ Additionally, there are multiple ICD-10-CM codes for anxiety disorders.⁴⁷ Because anxiety maintains a common definition in the medical community and has ICD-10-CM codes, I find that anxiety is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. From my review of this condition, the generally accepted treatments for anxiety are dependent on the symptoms and the severity of the particular disorder. Mild and moderate forms of anxiety may not require a pharmacologic intervention, but may necessitate other forms of treatment, such as meditation, mindfulness, breathing techniques as well as psychotherapy (counseling) or cognitive therapy.⁴⁸ The most common classes of medications used to combat anxiety disorders are antidepressants, anti-anxiety drugs, and beta-blockers.⁴⁹ Antidepressants are safe and effective but they may be risky for children, teens, and young adults.⁵⁰ Antidepressants also come with a "black box" warning – the FDA's strongest warning - advising that some people may have suicidal thoughts or make suicide attempts while taking the medication.⁵¹ The most common anti-anxiety medications are called benzodiazepines. As noted by the Panel, the common side effects of benzodiazepines include headache, confusion, tiredness, and in some cases nightmares and memory impairments.⁵² And, benzodiazepines carry a risk of dependence and addiction.⁵³ Furthermore, the FDA notes that the number of patients who were prescribed both an opioid analgesic and benzodiazepine increased by 41% between 2002 and 2014.⁵⁴ As a result, the FDA requires black box warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines to inform the patient about the serious risks associated with using these medications at the same time.⁵⁵ Thus, I find that the treatments for anxiety are recognized and accepted by the medical community as the treatments for this condition and relate to the suffering of the patient.

⁴⁵ See <https://dsm.psychiatryonline.org/doi/abs/10.1176/appi.books.9780890425596.dsm05> (last visited March 13, 2018).

⁴⁶ Ibid.

⁴⁷ See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited March 13, 2018).

⁴⁸ See <https://adaa.org/finding-help/treatment#> (last visited March 14, 2018).

⁴⁹ Ibid.

⁵⁰ See <https://www.mayoclinic.org/diseases-conditions/teen-depression/in-depth/antidepressants/art-20047502> (last visited March 14, 2018).

⁵¹ Ibid.

⁵² See <https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml> (March 14, 2018).

⁵³ Ibid.

⁵⁴ See <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm> (last visited March 14, 2018).

⁵⁵ Ibid.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the anxiety condition itself as well as the treatments for this condition cause severe suffering for patients. Specifically, anxiety may lead to problems that negatively impact an individual's activities of daily living and quality of life and may lead to suicide and depression. Anxiety disorders can also cause significant distress or interfere with social, occupational, and other areas of functioning. In fact, an estimated 31.1% of U.S. adults experience an anxiety disorder at some time in their lives.⁵⁶ Medications, in some instances, may exacerbate the symptoms and are associated with debilitating side effects that can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that both the condition of anxiety as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. As discussed above, mild and moderate forms of anxiety may be treated with meditation, mindfulness, breathing techniques as well as counseling or cognitive therapy that can be effective. Progression to medication therapy may be initiated; however, in both instances, one must consider the therapeutic response. Failure to respond to therapies or side effects associated with treatments may result in significant impacts on quality of life. As such, I find that there is an absence of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for migraine that cause suffering.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that cannabis is generally accepted as an effective treatment for anxiety. The Panel discussed medical evidence that cannabis may exacerbate anxiety symptoms or that an effect related to cannabis may be associated with anxiety, such as dependence and cravings. Literature suggests that individuals with anxiety sensitivity may be more likely to turn to cannabis as a mechanism for coping with stress, which may in turn lead to problematic use behaviors.⁵⁷ However, the Panel further discussed a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, which found that there is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, which was assessed by a public speaking test utilizing individuals with social anxiety disorders.⁵⁸ On balance, the Panel recommended adding anxiety as an allowable condition under the MMP as research suggests that it could be helpful to some patients with this condition. I agree. While marijuana may not be effective for all anxiety sufferers, there is research evidencing that it may be helpful to some, especially those with social anxiety disorders. Thus, I find that there is acceptance in the medical community that marijuana is likely to relieve the suffering associated with some anxiety conditions. However, like any medical condition, the use of medical marijuana to treat anxiety must be explored by the

⁵⁶ See <https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml> (last visited March 13, 2018).

⁵⁷ Anxiety Sensitivity and Distress Intolerance as Predictors of Cannabis Dependence Symptoms, Problems, and Craving: The Mediating Role of Coping Motives. Farris SG, Metrik J, Bonn-Miller MO, Kahler CW, Zvolensky MJ. *J Stud Alcohol Drugs*. 2016 Nov;77(6):889-897.

⁵⁸ The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research, National Academies Press (2017); Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials, *British Journal of Clinical Pharmacology* (2001).

medical professional treating the patient to determine whether it is the best and most appropriate course of treatment for the patient.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of anxiety under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of anxiety is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that anxiety should be added to the MMP.

Denied Petitions

Asthma

After carefully reviewing the petition seeking to include asthma as a debilitating condition under the MMP, and in accordance with the Panel’s recommendation, I am denying the request. In coming to this conclusion, I reviewed the petition against the six regulatory factors cited above and found that the condition fails to meet the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that asthma meets this requirement. The CDC defines asthma as a chronic lung disease⁵⁹ that “causes repeated episodes of wheezing, breathlessness, chest tightness, and nighttime or early morning coughing.”⁶⁰ Moreover, the Department recognizes asthma as a chronic medical condition with approximately 600,000 adults and 167,000 children suffering from this condition in New Jersey.⁶¹ Thus, I find that asthma is generally accepted by the medical community as a valid medical condition.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. In the petition, the petitioner asserts that the use of albuterol to treat asthma causes an individual to experience an increased heart rate and shakiness and that the use of corticosteroids to treat asthma can cause the patient to become addicted to the drug. While corticosteroids and bronchodilators, such as albuterol, are generally accepted treatments for asthma, I do not find that the average patient suffers from the use of these medications. As stated by the Panel, there are several treatments for asthma that are not only effective but also provide minimal side effects. Specifically, asthma is generally treated with inhaled, oral and intravenous corticosteroids and bronchodilators.⁶² Common side effects associated with the use of corticosteroids include acne, weight gain and upset stomach.⁶³ However, these side effects rarely occur with the short-term use of these medications, such as when they are used for acute asthma episodes.⁶⁴ While the use of corticosteroids is accepted

⁵⁹ See https://www.cdc.gov/asthma/stateprofiles/asthma_in_nj.pdf (last visited March 13, 2018).

⁶⁰ See <https://www.cdc.gov/asthma/default.htm> (last visited March 13, 2018).

⁶¹ See <http://www.nj.gov/health/fhs/chronic/asthma/in-nj/> (last visited March 13, 2018).

⁶² See <https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660> (last visited March 13, 2018).

⁶³ See <https://my.clevelandclinic.org/health/diseases/16864-treating-the-inflammation-of-asthma> (last visited March 13, 2018).

⁶⁴ Ibid.

by the medical community as valid treatments for asthma, I do not find that these treatments cause the vast majority of patients to experience suffering from their use.

The same holds true for bronchodilators. While bronchodilators can cause nervousness or shakiness, headache, throat or nasal irritation, muscle aches and, in rare instances, a rapid heart rate or heart palpitations, these side effects can be greatly reduced and even eliminated by changing the delivery method of the medication and/or reducing the dosage.⁶⁵ Although these side effects could potentially cause a patient to suffer, they can be effectively decreased and even eliminated through medication management. As such, I find that the treatments for asthma do not cause an average asthma patient to experience suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that asthma can cause severe suffering. Specifically, when asthma is not well-controlled, it can severely impair a patient's ability to engage in his or her activities of daily living, such as limiting the patient's physical activity, cause sleep disturbances and can even result in death. Accordingly, I find that asthma can cause a patient to experience severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. While asthma cannot be cured, it can be well-controlled with self-management education, adequate pharmacological management, and avoidance of exposure to environmental triggers.⁶⁶ Specifically, asthma is commonly and effectively treated with bronchodilators and corticosteroids, which are widely available to patients and have little side effects.⁶⁷ Thus, I find that the conventional medical treatments for asthma are effective and easily attainable by patients.

Regarding the fifth factor, which whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there are no reliable clinical trials or research supporting the proposition that medical cannabis is an effective treatment for asthma. While the petitioner points to a study published in the New England Journal of Medicine in 1973, which suggests that marijuana dilates the airway for a short period of time, the study did not evaluate the effect marijuana has on patients suffering from asthma. In fact, the study utilized thirty-two male subjects with no serious medical conditions and advised that "further investigation is required to determine . . . the effects of marijuana smoking and oral THC on the airway of asthmatic subjects." As such, I find that this study does not support the proposition that marijuana is an effective treatment for asthma.

Even more, physicians with the American Thoracic Society recently published an article in the American Journal of Respiratory and Critical Care Medicine advising that marijuana can worsen existing lung conditions and specifically noted that "marijuana smoke can cause an

⁶⁵ See <https://www.mayoclinic.org/diseases-conditions/asthma-attack/expert-answers/albuterol-side-effects/faq-20058088> (last visited March 13, 2018).

⁶⁶ See <https://www26.state.nj.us/doh-shad/topic/Asthma.html> (last visited March 13, 2018).

⁶⁷ See Footnote 62.

asthma attack leading to hospitalization and even death.⁶⁸ Thus, the medical community appears to be opposed to the use of marijuana as a treatment for asthma. Because the petitioner failed to point to any evidence demonstrating that the medical community accepts medical marijuana as a treatment for asthma, and neither I nor the Panel found any reliable trials or research in support of this, I find that the medical community is not in favor of using medicinal cannabis to alleviate the suffering associated with asthma.

As for the final factor, which is whether there are letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of asthma under the MMP, I find that the petition only referenced the 1973 New England Journal of Medicine article and did not include any letters of support from healthcare professionals. While the journal article was authored by three physicians, I do not find that this lone article from 1973 on the general effects of marijuana on the airway constitutes support from a medical professional for the inclusion of asthma to the MMP. Additionally, there were no public comments from medical professionals supporting the inclusion of asthma under the MMP. Thus, I find that there is a lack of support from physicians or other health care professionals for this condition to be added to the MMP.

Based upon the foregoing, I find that asthma can be debilitating if uncontrolled, but that marijuana is not likely to be a beneficial treatment for this condition or alleviate the debilitating effect of this condition. Indeed, as noted by the Panel, inhalation of smoke is a known trigger for asthma exacerbation and, as a result, smoking marijuana may actually increase the suffering of asthma patients rather than alleviate the suffering associated with this condition⁶⁹. And, while I acknowledge that medicinal marijuana is available in non-smokable forms, I am not convinced that there is credible support for its use in treating asthma. Unless and until there is sufficient research and evidence demonstrating that the use of marijuana can be beneficial for an asthma patient, I find that asthma should not be added to the MMP.

Chronic Fatigue Syndrome

From my detailed review of the petition seeking to include chronic fatigue syndrome as a debilitating condition under the MMP, and in accordance with the Panel's recommendation, I have concluded that the petition should be denied. In coming to this conclusion, I reviewed the petition against the six regulatory factors cited above and found that the condition fails to meet the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic fatigue syndrome meets this criteria. According to the CDC, chronic fatigue syndrome, also known as myalgic encephalomyelitis, is a "long-term illness that affects many body systems."⁷⁰ In addition to extreme fatigue, which may worsen with physical or mental activity, but does not improve with rest, an individual with this condition may experience insomnia, depression, joint and muscle pain and memory impairments.⁷¹ In fact, there is an estimated 836,000 to 2.5 million individuals

⁶⁸ Drake MD, Matthew G. and Slatore MD, Christopher G. "Smoking Marijuana and the Lungs." Am. J. Respir. Crit. Care Med., Vol. 195, P5-6 (2017).

⁶⁹ *Ibid.*

⁷⁰ <https://www.cdc.gov/me-cfs/index.html> (last visited March 13, 2018).

⁷¹ <https://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/symptoms-causes/syc-20360490> (last visited March 13, 2018).

affected with this condition in the United States.⁷² Thus, I find that chronic fatigue syndrome is a valid medical condition.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. Unfortunately, there is neither a cure nor an FDA-approved treatment for chronic fatigue syndrome.⁷³ As a result, treatment is largely palliative as the treatment is tailored to relieve the symptoms experienced by each individual patient. For example, a patient experiencing depression as a result of chronic fatigue syndrome could be treated with an anti-depressant and a patient experiencing muscle and joint pain could be prescribed an NSAID to relieve the pain.⁷⁴ Moreover, the symptoms of chronic fatigue are oftentimes treated with nutritional supplements and complementary therapies, such as massage, meditation, tai chi and acupuncture, which may be helpful in increasing the patient's energy level and decreasing his or her pain.⁷⁵ But, these are not treatments for the actual condition but rather treatments for the symptoms associated with the condition. As such, I find that there is no treatment generally accepted in the medical community for this disease that causes suffering.

However, I do find that the above therapies prescribed by healthcare professionals to treat the **symptoms** associated with chronic fatigue syndrome are accepted by the medical community. While I find that the treatments for chronic fatigue symptoms are medically acceptable, the specific treatment prescribed depends on the type and severity of the symptoms presented and can range from anti-depressants and NSAIDs, which can have severe side effects for some patients and thereby cause suffering, to massage therapy and acupuncture, which have little to no side effects. Because there is a vast array of treatment options for chronic fatigue symptoms and no two patients are treated the same, I am unable to conclude that chronic fatigue patients generally suffer from the treatments they receive for their symptoms. However, individuals with severe forms of chronic fatigue syndrome may suffer from the treatments used to alleviate their symptoms.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that chronic fatigue syndrome can cause severe suffering. Specifically, some individuals suffering from chronic fatigue syndrome can experience severe pain, gross memory loss and even such extreme fatigue that the patient is house-bound or even bed-bound, all of which greatly impacts a patient's ability to engage in activities of daily living and maintain a quality life. Accordingly, I find that chronic fatigue syndrome can cause a patient to experience severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. While chronic fatigue cannot be cured and there is no approved treatment for the condition, there is a wide array of pharmacological therapies available for alleviating the symptoms associated with this condition. Specifically, chronic fatigue symptoms

⁷² Wright Clayton, MD, Ellen, "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome An IOM Report on Redefining an Illness." JAMA (2015).

⁷³ <https://www.cdc.gov/me-cfs/treatment/index.html> (last visited March 13, 2018).

⁷⁴ <https://www.cdc.gov/me-cfs/index.html> (last visited March 13, 2018).

⁷⁵ Ibid.

can be effectively managed for some patients with NSAIDs, anti-depressants and sleep-aids, depending on the severity and type of symptoms presented. However, depending upon the patient, the pharmacological treatments for chronic pain symptoms may be effective but may also cause the patient to suffer from side effects. Thus, I find that there are available conventional medical therapies to alleviate a chronic fatigue patient's suffering, but those treatments may cause suffering for some patients.

Regarding the fifth factor, whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there are no reliable clinical trials or research supporting the proposition that medical cannabis is an effective treatment for chronic fatigue syndrome. While the petitioner points to studies suggesting that medical marijuana can alleviate an individual's pain, which is potentially one symptom a patient inflicted with chronic fatigue syndrome may experience, the studies fail to articulate that marijuana is an effective treatment for the condition of chronic fatigue syndrome as a whole. Because the petitioner failed to point to any evidence demonstrating that the medical community accepts medical marijuana as a treatment for the actual condition of chronic fatigue syndrome, and neither I nor the Panel found any credible clinical evidence in support of this, I find that there is a lack of support in the medical community for the use of medicinal cannabis to alleviate the suffering associated with chronic fatigue syndrome.

As for the final factor, which is whether there are letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic fatigue under the MMP, I find that the petition only referenced the above-mentioned studies reflecting on the effectiveness of medical marijuana to treatment pain and did not include any letters of support from healthcare professionals to have chronic fatigue added to the MMP. Additionally, there was an absence of public comments from medical professionals supporting the inclusion of chronic fatigue under the MMP. Thus, I find that there is a lack of support from physicians or other health care professionals for this condition to be added to the MMP.

Based upon the above analysis, I find that chronic fatigue syndrome can be debilitating for some patients, but that medical marijuana is not likely to be a potentially beneficial treatment for the debilitating effect of this condition or the alleviation of the symptoms associated with this condition. Indeed, as noted by the Panel, this condition has been researched for years and there is yet to be found a solid elucidation of the etiology of this condition or the treatments that are effective for it.⁷⁶ Because there are still so many unknowns with this condition and there is no clinical evidence suggesting that marijuana would be beneficial as a treatment, I find that chronic fatigue syndrome should not be added to the MMP at this time.

Conclusion

Based upon the foregoing, I am adding chronic pain associated with musculoskeletal disorders, chronic pain of a visceral origin, as well as Tourette's Syndrome, migraine, and anxiety to the MMP. However, asthma and chronic fatigue syndrome will not be added to the MMP.

In order to provide patients with relief as soon as possible from the suffering they are experiencing from these debilitating conditions, I am immediately adding chronic pain associated with musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety to the MMP in advance of rule promulgation. While I am including these conditions

⁷⁶ <https://www.ncbi.nlm.nih.gov/books/NBK293931/> (last visited March 13, 2018).

under the MMP, please note that this decision is not intended to be a blanket endorsement for every patient inflicted with a condition falling under the MMP to utilize medicinal marijuana as a treatment. As with any condition, the course of treatment must be determined by a medical professional after a thorough evaluation and discussion with the patient regarding the benefits and possible negative effects of the recommended therapy. Accordingly, I encourage patients to discuss the possibility of utilizing medical marijuana as a treatment for their debilitating conditions with the medical professionals treating them. I hope that this decision brings needed relief to those suffering with these conditions.

This is a final agency decision. You have the right to appeal this final agency decision within 45 days to the New Jersey Superior Court, Appellate Division, Richard J. Hughes Justice Complex, P.O. Box 006, Trenton, New Jersey 08625-0006.



Shereef M. Elnahal, MD, MBA
Acting Commissioner

Question 2

Relevant medical or scientific evidence pertaining to the disease
or condition

Contents

Overview – 3

Generalized Anxiety Disorder: When Worry Gets Out of Control – National Institute of Mental Health - 4

Overview

General Anxiety Disorder (GAD) is a mental health disorder that can interfere significantly in a patient's daily life

Generalized anxiety disorder symptoms can vary. They may include:

- Persistent worrying or anxiety about a number of areas that are out of proportion to the impact of the events
- Overthinking plans and solutions to all possible worst-case outcomes
- Perceiving situations and events as threatening, even when they aren't
- Difficulty handling uncertainty
- Indecisiveness and fear of making the wrong decision
- Inability to set aside or let go of a worry
- Inability to relax, feeling restless, and feeling keyed up or on edge
- Difficulty concentrating, or the feeling that your mind "goes blank"

Physical signs and symptoms may include:

- Fatigue
- Trouble sleeping
- Muscle tension or muscle aches
- Trembling, feeling twitchy
- Nervousness or being easily startled
- Sweating
- Nausea, diarrhea or irritable bowel syndrome
- Irritability

Treatments include:

- Psychotherapy including cognitive behavioral therapy
- Medication

GAD is a debilitating disease that is difficult to treat, and it is vital for a patient's quality of life that they're physician have access to all credible treatments, including medical marijuana.

WHAT IS GAD?

Occasional anxiety is a normal part of life. You might worry about things like health, money, or family problems. But people with generalized anxiety disorder (GAD) feel extremely worried or feel nervous about these and other things—even when there is little or no reason to worry about them. People with GAD find it difficult to control their anxiety and stay focused on daily tasks.

The good news is that GAD is treatable. Call your doctor to talk about your symptoms so that you can feel better.

What are the signs and symptoms of GAD?

GAD develops slowly. It often starts during the teen years or young adulthood. People with GAD may:

- Worry very much about everyday things
- Have trouble controlling their worries or feelings of nervousness
- Know that they worry much more than they should
- Feel restless and have trouble relaxing
- Have a hard time concentrating
- Be easily startled
- Have trouble falling asleep or staying asleep
- Feel easily tired or tired all the time
- Have headaches, muscle aches, stomach aches, or unexplained pains
- Have a hard time swallowing
- Tremble or twitch
- Be irritable or feel “on edge”
- Sweat a lot, feel light-headed or out of breath
- Have to go to the bathroom a lot

Children and teens with GAD often worry excessively about:

- Their performance, such as in school or in sports
- Catastrophes, such as earthquakes or war



Adults with GAD are often highly nervous about everyday circumstances, such as:

- Job security or performance
- Health
- Finances
- The health and well-being of their children
- Being late
- Completing household chores and other responsibilities

Both children and adults with GAD may experience physical symptoms that make it hard to function and that interfere with daily life.

Symptoms may get better or worse at different times, and they are often worse during times of stress, such as with a physical illness, during exams at school, or during a family or relationship conflict.

What causes GAD?

GAD sometimes runs in families, but no one knows for sure why some family members have it while others don't. Researchers have found that several parts of the brain, as well as biological processes, play a key role in fear and anxiety. By learning more about how the brain and body function in people with anxiety disorders, researchers may be able to create better treatments. Researchers are also looking for ways in which stress and environmental factors play a role.

How is GAD treated?

First, talk to your doctor about your symptoms. Your doctor should do an exam and ask you about your health history to make sure that an unrelated physical problem is not causing your symptoms. Your doctor may refer to you a mental health specialist, such as a psychiatrist or psychologist.

GAD is generally treated with psychotherapy, medication, or both. Talk with your doctor about the best treatment for you.

Psychotherapy

A type of psychotherapy called cognitive behavioral therapy (CBT) is especially useful for treating GAD. CBT teaches a person different ways of thinking, behaving, and reacting to situations that help him or her feel less anxious and worried. For more information on psychotherapy, visit <http://www.nimh.nih.gov/health/topics/psychotherapies>.

Medication

Doctors may also prescribe medication to help treat GAD. Your doctor will work with you to find the best medication and dose for you. Different types of medication can be effective in GAD:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Other serotonergic medication
- Benzodiazepines

Doctors commonly use SSRIs and SNRIs to treat depression, but they are also helpful for the symptoms of GAD. They may take several weeks to start working. These medications may also cause side effects, such as headaches, nausea, or difficulty sleeping. These side effects are usually not severe for most people, especially if the dose starts off low and is increased slowly over time. **Talk to your doctor about any side effects that you have.**

Buspirone is another serotonergic medication that can be helpful in GAD. Buspirone needs to be taken continuously for several weeks for it to be fully effective.

Benzodiazepines, which are sedative medications, can also be used to manage severe forms of GAD. These medications are powerfully effective in rapidly decreasing anxiety, but they can cause tolerance and dependence if you use them continuously. Therefore, your doctor will only prescribe them for brief periods of time if you need them.

Don't give up on treatment too quickly. Both psychotherapy and medication can take some time to work. A healthy lifestyle can also help combat anxiety. Make sure to get enough sleep and exercise, eat a healthy diet, and turn to family and friends who you trust for support.

For basic information about these and other mental health medications, visit <http://www.nimh.nih.gov/health/topics/mental-health-medications>. Visit the Food and Drug Administration's website (<http://www.fda.gov/>) for the latest information on warnings, patient medication guides, or newly approved medications.

What is it like to have GAD?

"I was worried all the time and felt nervous. My family told me that there were no signs of problems, but I still felt upset. I dreaded going to work because I couldn't keep my mind focused. I was having trouble falling asleep at night and was irritated at my family all the time.

I saw my doctor and explained my constant worries. My doctor sent me to someone who knows about GAD. Now I am working with a counselor to cope better with my anxiety. I had to work hard, but I feel better. I'm glad I made that first call to my doctor."

Where can I find more information?

To learn more about generalized anxiety disorder, visit:

MedlinePlus (National Library of Medicine)

<http://medlineplus.gov>

(En Español: <http://medlineplus.gov/spanish>)

For information on clinical trials, visit:

ClinicalTrials.gov

<http://www.clinicaltrials.gov>

(En Español: <http://salud.nih.gov/investigacion-clinica/>)

For more information on conditions that affect mental health, resources, and research, visit the NIMH website (<http://www.nimh.nih.gov>).

National Institute of Mental Health (NIMH)

Office of Science Policy, Planning,

and Communications

Science Writing, Press,

and Dissemination Branch

6001 Executive Boulevard

Room 6200, MSC 9663

Bethesda, MD 20892-9663

Phone: 301-443-4513 or

1-866-615-NIMH (6464) toll-free

TTY: 301-443-8431 or

1-866-415-8051 toll free

Fax: 301-443-4279

Email: nimhinfo@nih.gov

Website: <http://www.nimh.nih.gov>



National Institute
of Mental Health

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Institutes of Health
NIH Publication No. QF 16-4677
Revised 2016



Question 5

Letters of support provided by physicians with knowledge of the disease or condition.

To Whom It May Concern,

We, the undersigned physicians, support adding generalized anxiety disorder to the qualifying conditions list under Ohio's Medical Marijuana Control Program.

We have reviewed the available science, research and information on treating generalized anxiety disorder with medical marijuana and believe it to be an effective treatment, and that the benefits outweigh the risks.

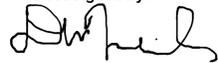
Any physician who has treated a patient with generalized anxiety disorder understands the immense impact this condition can have on a person's quality of life. At its most severe, generalized anxiety disorder can leave a patient bedridden and unable to perform basic daily tasks.

[Studies conducted by Tyrer and Baldwin in 2006 and Yonkers *et al* in 1996 have shown remission rates for generalized anxiety disorder are low.](#)

Given the difficulty of treating this condition, and the detrimental nature of it on a patient's life, we believe adding medical marijuana to the list of treatment options is vital to patient wellbeing.

For these reasons, we ask that the State Medical Board of Ohio add generalized anxiety disorder as a qualifying condition under Ohio's Medical Marijuana Control Program.

Sincerely,

DocuSigned by:

FED24AE73239452...

Daniel Neides

MD

To Whom It May Concern,

We, the undersigned physicians, support adding generalized anxiety disorder to the qualifying conditions list under Ohio's Medical Marijuana Control Program.

We have reviewed the available science, research and information on treating generalized anxiety disorder with medical marijuana and believe it to be an effective treatment, and that the benefits outweigh the risks.

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Sincerely,

DocuSigned by:

D930A4595010472...

Cynthia Taylor

do

Question 3

Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition

Contents

Overview – 3

Generalised Anxiety Disorder in Adults: Management in Primary, Secondary and Community Care.– 4

Achieving Remission in Generalized Anxiety Disorder – 16

Overview

General Anxiety Disorder (GAD) is a mental health disorder characterized by excessive worry and other symptoms ranging from restlessness to irritability. For many patients, chronic GAD can be debilitating, and at its worst leave a patient unable to go about their daily life.

Treating GAD is complicated by the fact that it is often associated with other conditions and sufferers regularly go years without seeking treatment. Nonetheless, when patients do seek treatment, they're results vary based on a range of factors with only 50-60% responding clinically to therapy and even less entering remission.

Attached are two publications detailing both the difficulties in treating GAD and the success rates of current treatment options:

1. **Generalised Anxiety Disorder in Adults: Management in Primary, Secondary and Community Care** – “Most clinical studies suggest that GAD is typically a chronic condition with low rates of remission over the short and medium-term. Evaluation of prognosis is complicated by the frequent comorbidity with other anxiety disorders and depression, which worsen the long-term outcome and accompanying burden of disability (Tyrer & Baldwin, 2006).”
2. **Achieving Remission in Generalized Anxiety Disorder** - “Between 50% and 60% of patients respond clinically to therapy, but only one-third to one-half attain remission or realize full recovery during the acute phase of treatment.”

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2 GENERALISED ANXIETY DISORDER

2.1. INTRODUCTION

[Go to:](#)

This guideline is concerned with the treatment and management of adults with a diagnosis of GAD in primary and secondary care. GAD is one of a range of anxiety disorders including panic disorder (with and without agoraphobia), PTSD, OCD, social phobia, specific phobias (for example, of spiders) and acute stress disorder.

GAD commonly coexists with other anxiety disorders and with depressive disorders, as well as a variety of physical health disorders. 'Pure' GAD in the absence of another anxiety or depressive disorder is less typical than comorbid GAD. This guideline is relevant to both people with pure and comorbid GAD. The NICE guideline on case identification and referral for common mental health disorders will provide further guidance on identification ([NICE, 2011](#)).

2.2. THE DISORDER

[Go to:](#)

2.2.1. Symptoms, presentation and patterns of illness

Anxiety is a prominent symptom of many psychiatric disorders but it is only comparatively recently that several distinct anxiety disorders have been recognised in classificatory systems. The key feature of GAD is worry and apprehension that is out of proportion to the circumstances. The worries are typically widespread, involve everyday issues and have a shifting focus of concern. The affected person finds the worries difficult to control, and this can result in decreased occupational and social functioning ([Tyrrer & Baldwin, 2006](#); [Bitran et al., 2009](#)).

As well as worry that is excessive, generalised and difficult to control, people with GAD experience other psychological and somatic symptoms of anxiety. Psychological symptoms include irritability, poor concentration, increased sensitivity to noise and sleep disturbance, typically difficulty falling asleep. Somatic symptoms of GAD can manifest in many different ways. For example, an overactive autonomic nervous system can lead to sweating, dry mouth, palpitations, urinary frequency, epigastric discomfort and frequent and/or loose bowel motions, while hyperventilation may result in feelings of shortness of breath and dizziness. Increased muscle tension is a common accompaniment of persistent anxiety and may be experienced as restlessness, inability to relax, headaches and aching pains, particularly in the shoulders and back ([Gelder et al., 2006](#)).

GAD is frequently comorbid with other mental disorders, which can complicate its presentation. The rates of comorbidity vary between studies with estimates of between 68 and 93% of comorbidity with another axis 1 mental health disorder ([Carter et al., 2001](#); [Hunt et al., 2002](#); [ESEMED/MHEDEA 2000 Investigators, 2004](#)). Comorbid disorders that are particularly common include depressive disorders (specifically major depression and dysthymia), other anxiety disorders (especially panic disorder, social phobia and specific phobias) and somatoform disorders ([Bitran et al., 2009](#); [Carter et al., 2001](#); [Hunt et al., 2002](#); [Grant et al., 2005](#); [Kessler et al., 2005b](#)). There is also significant comorbidity with substance misuse especially among men ([Grant et al., 2005](#); [Kessler et al., 2005b](#)).

GAD also often co-occurs with physical health problems such as arthritis and gastrointestinal and respiratory disorders and may mimic the presentation of some

In this Page

[INTRODUCTION](#)[THE DISORDER](#)[AETIOLOGY](#)[TREATMENT AND MANAGEMENT IN THE NHS](#)

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physical conditions (for example, hyperthyroidism) (Culpepper, 2009; Roy-Byrne *et al.*, 2008; Sareen *et al.*, 2006). Due to the somatic symptoms of anxiety, which are central to GAD, and physical comorbidities, people with GAD who present in primary care may emphasise somatic problems or sleep disturbance, rather than excessive worry or psychological symptoms of anxiety (Rickels & Rynn, 2001).

2.2.2. Course and prognosis

Most clinical studies suggest that GAD is typically a chronic condition with low rates of remission over the short and medium-term. Evaluation of prognosis is complicated by the frequent comorbidity with other anxiety disorders and depression, which worsen the long-term outcome and accompanying burden of disability (Tyrer & Baldwin, 2006). In the Harvard-Brown Anxiety Research Program, which recruited participants from Boston hospitals, the mean age of onset of GAD was 21 years, although many participants had been unwell since their teens. The average duration of illness in this group was about 20 years and despite treatment the outcome over the next 3 years was relatively poor, with only one in four showing symptomatic remission from GAD (Yonkers *et al.*, 1996). The proportion of people who became free from all psychiatric symptomatology was smaller, about one in six. In people who remitted from GAD the risk of relapse over the next year was about 15%, increasing to about 30% in those who achieved only partial symptomatic remission (Yonkers *et al.*, 1996).

The participants in the above study were recruited from hospital services and may not be representative of GAD in general. In a naturalistic study in the UK, Tyrer and colleagues (2004) followed up people with anxiety and depression identified in psychiatric clinics in primary care and found that 12 years later 40% of those initially diagnosed with GAD had recovered, in the sense that they no longer met criteria for any *Diagnostic and Statistical Manual of Mental Disorders* 3rd edition (DSM-III; American Psychiatric Association [APA], 1980) psychiatric disorder. The remaining participants remained symptomatic, but GAD was still the principal diagnosis in only 3% of trial participants; in the vast majority conditions such as dysthymia, major depression and agoraphobia were now more prominent. This study confirms the chronic and fluctuating symptomatic course of GAD in clinically-identified people. It should be noted, however, that the majority of people with GAD in the community do not seek medical help for their symptoms (Wittchen & Jacobi, 2005), and the course of the illness in these circumstances is not established.

2.2.3. Disability and mortality

As is the case with major depression, GAD is associated with a substantial burden of disability, equivalent to that of other chronic conditions such as arthritis and diabetes (Wittchen, 2002). Outcome studies suggest that anxiety disorders are more chronic than other common mental disorders (Tyrer *et al.*, 2004) and there is evidence that comorbid depression and anxiety has a worse prognosis, with more associated disability and more persistent symptoms than either depression or anxiety disorders alone (Kroenke *et al.*, 2007). There is also evidence in the community that anxiety disorders are independently associated with several physical conditions, and this comorbidity is significantly associated with poor quality of life and disability (Sareen *et al.*, 2006). This morbidity comes with high associated health and social costs (Simon *et al.*, 1995).

Studies have shown that the presence of GAD is also associated with significant impairments in occupational and social functioning. For example, over 30% of people with GAD showed an annual reduction of work productivity of 10% or more compared with 8% of people with major depression. The figure for people with comorbid GAD and depression was over 45% (Wittchen *et al.*, 2000). A large part of the economic cost of anxiety disorders is attributable to the costs of non-medical psychiatric treatment. People with GAD have increased numbers of visits not only to primary care doctors but also to hospital specialists, particularly gastroenterologists (Kennedy & Schwab, 1997; Wittchen, 2002). This may be a consequence of the distressing somatic symptoms which many people with GAD experience.

GAD also carries a considerable cost in personal suffering – in the Harvard-Brown Anxiety Research Program noted above, one third of people had never married and unemployment was higher than average (Yonkers *et al.*, 1996). Suicidal ideation and suicide attempts are significantly increased in GAD compared with the general population, particularly in women, and this increase is still greater in the presence of comorbid major depression (Cougler *et al.*, 2009).

2.2.4. Incidence and prevalence

The estimated proportion of people in England with GAD was 4.4% in the most recent *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009), a figure that has varied little across the three survey years 1993, 1997 and 2007. This figure is at the upper end of estimates of point and annual prevalence of 2.1 to 4.4% in English speaking countries (Grant *et al.*, 2005; Hunt *et al.*, 2002; Kessler & Wang, 2008) with lower rates of 0.8 to 2.2% reported from other European countries (Lieb *et al.*, 2005; Wittchen & Jacobi 2005). Worldwide estimates of the proportion of people who are likely to experience GAD in their lifetime vary between 0.8% and 6.4% (Lieb *et al.*, 2005; Grant *et al.*, 2005; Kessler & Wang, 2008).

Prevalence rates have generally been found to be between 1.5 and 2.5 times higher in women than men. In the *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009), the rates were 3.4% for men and 5.3% for women. In terms of age, epidemiological studies have generally found GAD to be less common in older age groups (over 55 years) although there are some exceptions. Some studies have also found GAD to be less common in younger adults (younger than 35 years).

Evidence from the US on ethnicity and race differences in GAD rates is inconsistent, with studies finding increased (Blazer *et al.*, 1991), decreased (Grant *et al.*, 2005) and no difference (Wittchen *et al.*, 1994) in rates between white and one or more of black, Asian and Hispanic groups. Numbers of minority ethnic groups sampled in the *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009) were too small to draw conclusions about possible differences, although proportions of the black and South Asian groups with GAD in the sample (both male and female) were higher than the equivalent proportions for white interviewees.

Socioeconomic factors associated with GAD are lower household income (Grant *et al.*, 2005; McManus *et al.*, 2009), lack of tertiary qualifications (Hunt *et al.*, 2002) and unemployment (Hunt *et al.*, 2002). Divorce, separation and death of a partner are also associated with an increased likelihood of GAD.

2.2.5. Diagnosis

Diagnostic criteria and methods of classification of anxiety disorders have changed substantially over the years. Historically what we now consider to be GAD was subsumed under 'anxiety neurosis'. It first appeared as a separate diagnosis in 1980 with the introduction of DSM-III (APA, 1980). In DSM-III it was a residual category to be used only when an anxiety disorder could not be classified under another diagnosis. It was only with the DSM-III revision in 1987 (DSM-III-R; APA, 1987) that it became a well defined condition in its own right. DSM-III-R also changed the DSM-III minimum duration requirement from 1 month to 6 months and introduced excessive worry as a central feature. Some of the developments in DSM-III-R were later reflected in the *International Classification of Diseases – the Classification of Mental and Behavioural Disorders* 10th revision (ICD-10; World Health Organization [WHO], 1992), although without the same focus on worry. The introduction of DSM-IV in 1994 (APA, 1994) further streamlined and refined the criteria, in particular focusing less on somatic symptoms of anxiety and replacing the DSM-III-R criterion that the worry is 'unrealistic' with a criterion that the worry is 'difficult to control'.

DSM-IV and ICD-10 have overlapping but different diagnostic features for GAD. DSM-IV emphasises worry ('apprehensive expectation'), including the feature that the worry is difficult to control, while ICD-10 focuses more on somatic symptoms of

anxiety, particularly autonomic reactivity and tension. DSM-IV requires two major symptoms (6 months or more of excessive anxiety and worry, occurring on more days than not, about a number of events and activities and difficulty controlling the worry) and three or more additional symptoms from a list of six. ICD-10, as operationalised in the *ICD-10 Diagnostic Criteria for Research* (ICD-10-DCR; [WHO, 1993](#)), requires 6 months or more prominent tension, worry and feelings of apprehension, and four from a list of 22 symptoms, of which at least one must be from a list of four autonomic symptoms (palpitations, sweating, trembling, dry mouth).

In line with the previous guideline on GAD ([NICE, 2004a](#)) and other NICE guidelines on anxiety disorders and depression ([NICE, 2005a, b; 2009b](#)) the GDG used DSM-IV, rather than ICD-10 to define the diagnosis of GAD, because the evidence base for treatments nearly always uses DSM-IV.

As there is now greater recognition of the need to consider 'subthreshold' depression in terms of human and economic costs and the risk of future major depression ([Rowe & Rapaport, 2006](#)), there has also been recent attention given to subthreshold GAD. Relaxing the DSM-IV requirements of duration, excessive worry and/or three associated symptoms more than doubles the estimated prevalence of GAD ([Ruscio et al., 2007](#)). Cases of subthreshold GAD have similar but reduced comorbidities, with persistence, impairment and sociodemographic correlates all being significantly associated with an elevated risk of subsequent psychopathology ([Kessler et al., 2005a; Ruscio et al., 2007](#)). The implication is that, in clinical practice, identification of subthreshold GAD may be helpful for prevention of future disorder.

2.3. AETIOLOGY

Go to: 

The aetiology of GAD is multifactorial and involves psychological, social and biological factors. Interpretation of experimental data is complicated by changes in diagnostic practice and the frequent occurrence of comorbidity, particularly with major depression ([Yonkers et al., 1996](#)). On the other hand, anxiety (or more precisely, fear) is readily modelled in animal experimental studies, and the brain circuitry relevant to fear has been characterised in both animals and humans ([Engel et al., 2009](#)). One influential formulation ('the theory of triple vulnerability') regards GAD as arising from three distinct kinds of vulnerability: a generalised biological, a generalised psychological and a specific psychological vulnerability ([Barlow, 2000; Bitran et al., 2009](#)).

Anxiety disorders run in families. For example, a family study found that the risk of GAD in first-degree relatives of people with GAD was five times that in control groups ([Noyes et al., 1987](#)), although specific genes conferring vulnerability to GAD have not yet been reliably identified. Indeed the genes involved in the transmission of GAD appear to increase susceptibility to other anxiety disorders such as panic disorder and agoraphobia as well as major depression ([Kendler, 1996; Hettema et al., 2001; 2005](#)). There is also genetic overlap between GAD and the temperamental trait of neuroticism, which is itself a predisposing factor for GAD ([Hettema et al., 2004](#)). Overall the findings suggest that genetic factors play a significant though moderate role in the aetiology of GAD, that these factors predispose people to a range of anxiety and depressive disorders rather than GAD specifically, and that environmental factors are important in determining the nature of the emotional disorder experienced by a particular person.

Several environmental factors are known to predispose individuals to GAD. These can act remotely or as contemporaneous triggers to the disorder. For example, good parenting experiences are important in providing children with a secure base from which to explore the world, and problems in child-parent attachment have been linked to feelings of diminished personal control of potentially threatening events ([Barlow, 2000](#)). Such feelings could plausibly contribute to the risk of experiencing anxiety disorders. Studies suggest that adults with GAD report experiencing parental styles characterised by overprotection and lack of emotional warmth ([Silove et al., 1991](#)). Similar findings have been reported in other anxiety disorders and depression ([Parker et al., 1995](#)), which suggest that certain parenting

styles may act as a psychological vulnerability factor for a range of subsequent emotional disorders. Similar comments apply to other kinds of childhood adversity such as neglect, abuse, maternal depression and family disruption, which increase the risk of experiencing GAD in adulthood as well as other anxiety and depressive disorders ([Brown & Harris, 1993](#); [Halligan et al., 2007](#); [Safren et al., 2002](#)). More recent stressful life events are also known to be involved in the onset of emotional disorders including GAD ([Roemer et al., 1996](#)). A study by [Kendler and colleagues \(2003\)](#) showed that stressful life events characterised by loss increased the risk of both depression and GAD; however, life events characterised by 'danger' (where the full import of the event was yet to be realised) were more common in those who subsequently developed GAD.

Particular coping and cognitive styles also predispose individuals to the development of GAD, although it is not always easy to distinguish predisposition from the abnormal cognitions seen in the illness itself. As noted above, it is believed that people who lack a sense of control of events and personal effectiveness, perhaps through early life experiences, are more prone to anxiety disorders ([Barlow, 2000](#)). Such individuals may also demonstrate trait-like cognitive biases in the form of increased attention to potentially threatening stimuli, overestimation of environmental threat and enhanced memory of threatening material. This has been referred to as the 'looming cognitive style', which appears to be a general psychological vulnerability factor for a number of anxiety disorders ([Reardon & Nathan, 2007](#)). More recent cognitive formulations have focused on the process of worrying itself, which is of central importance in the diagnosis of GAD. Studies suggest that people at risk of GAD use worry as a positive coping strategy to deal with potential threats, whereby the person worries until they feel reassured that they have appraised all possible dangers and identified ways of dealing with them. However, this can lead to 'worry about worry', when individuals come to believe, for example, that worrying in this way, while necessary for them, is also uncontrollable and harmful. This 'metacognitive belief' may constitute a transitional stage between excessive, but normal, worrying and GAD ([Wells, 2005](#)).

Studies of both animal and human subjects suggest that the amygdala plays a central role in the processing of information relevant to threat and fear ([Le Doux, 2000](#)). Activation of the amygdala can occur prior to conscious appreciation of threat but there are strong connections between the amygdala and areas of prefrontal cortex involved in the conscious experience and regulation of emotion ([Le Doux, 2000](#); [Phillips et al., 2003](#)). Another structure involved in anxiety is the hippocampus, which is important in relating fearful memories to their environmental context ([Fanselow, 2000](#)). The hippocampus forms part of a 'behavioural inhibition system', which is activated by potential threats, and has the ability in these circumstances to suspend ongoing behaviours ([Gray, 1982](#)). Brain imaging studies of individuals with high trait anxiety and people with GAD have shown exaggerated responses in both the amygdala and prefrontal cortex during presentation of emotionally threatening stimuli ([Bishop et al., 2004](#); [Nitschke et al., 2009](#)). It is therefore possible that pre-existing abnormalities in this circuitry might predispose people to GAD and other anxiety disorders.

The neural circuitry involved in fear and anxiety is modulated by brain neurotransmitters and other chemical mediators including hormones ([Dedovic et al., 2009](#)). A relevant hormonal system is the hypothalamo-pituitary-adrenal axis (HPA), which regulates cortisol secretion. Adversity experienced in childhood and current stresses can alter the pattern of cortisol secretion in adult life, and there is an extensive literature on the role of HPA axis dysfunction in major depression (for example, [Pariante & Lightman, 2008](#)). HPA axis activity in people with GAD has been much less studied but there is some evidence that GAD, like depression, is associated with excessive glucocorticoid secretion ([Mantella et al., 2008](#)). The monoamine neurotransmitters, serotonin and noradrenaline, can alter fear processes in animals and have extensive inputs to the relevant neural circuitry, including the amygdala and the behavioural inhibition system ([Bitran et al., 2009](#); [Garner et al., 2009](#)). In addition, selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of GAD ([Baldwin et al., 2005](#)). Despite this there is only modest evidence that abnormalities in serotonin and noradrenaline are

involved in the pathophysiology of GAD, though more work needs to be carried out with ligand neuroimaging to resolve this issue ([Garner et al., 2009](#)). In the same way, pharmacological manipulation of gamma-aminobutyric acid (GABA) neurones and their associated benzodiazepine receptors clearly have profound effects on the experience of fear and anxiety in animals and humans ([Kalueff & Nutt, 2007](#)) but again there is only modest evidence that abnormalities in GABA neurotransmission or benzodiazepine receptor function are involved in the aetiology of GAD ([Garner et al., 2009](#)).

Overall there is good evidence that both genetic factors and early life difficulties can predispose people to a range of emotional disorders, including GAD. More specific risk factors for GAD, presumably occurring in combination with these more generalised vulnerabilities, include certain kinds of life events and particular individual cognitive styles involving the use of worrying as a coping strategy. The neural circuitry involved in fear and anxiety has been well delineated in brain imaging studies and abnormalities in both people with GAD and non-clinical subjects with high trait anxiety have been described in relevant brain regions. It seems likely that these neural changes are associated with abnormal cognitions, such as increased attention to threat, that are seen in people with GAD and those at risk of the disorder. There is much knowledge on how particular neuropharmacological manipulations can influence anxiety. While this information has proved helpful in developing pharmacological treatment, the role of neurotransmitters and other chemical mediators in the aetiology of GAD is currently unclear.

2.4. TREATMENT AND MANAGEMENT IN THE NHS

Go to: 

2.4.1. Detection, recognition and referral in primary care

Relative to its prevalence in the community, GAD is more common in primary care occurring in about 5% of attendees, and is the most common anxiety disorder seen in this setting. A recent international review of some of the larger general population surveys reported 12-month prevalence rates of 5.6 to 18.1% for anxiety disorders, of which GAD and panic disorder together accounted for over half of the prevalence figures ([Baumeister & Hartner, 2007](#)).

General practitioner (GP) rates of diagnosis and treatment of anxiety disorders are much lower than expected from the prevalence figures ([Wittchen & Jacobi, 2005](#)). [Wittchen and colleagues \(2002\)](#) found that recognition rates by primary care practitioners were only 34.4% for pure GAD and 43% for GAD with comorbid depression. There are likely to be a variety of reasons why GPs are poor at recognising anxiety disorders in their patients. People with GAD may have symptoms of anxiety, worry, tension, irritability or tiredness, about which they feel reluctant to complain to their GP because they do not view these symptoms as being 'medical', or the GP may identify these as symptoms of a more general malaise and not specifically consider or ask about anxiety as a possible cause ([Arroll & Kendrick, 2009](#)). In addition, many people may present with somatic symptoms associated with their anxiety, considering these to be more legitimate or more troubling. It appears that people with anxiety disorders are often frequent users of primary care resources, but if the anxiety component of their problem is not detected they may not receive the correct treatment and may undergo unnecessary and costly investigations, in particular for their physical symptoms ([Hales et al., 1997](#)). Recognition is increased by factors such as older age, presentation of other psychological problems, and enhanced knowledge, skills and attitudes of practitioners in primary care ([Tylee & Walters, 2007](#)).

There is evidence that GPs may not offer effective evidence-based treatments to people with anxiety disorders as often as may be indicated, and that the treatments offered are more likely to be pharmacological, rather than psychological therapies such as cognitive behavioural therapy (CBT) ([Stein et al., 2004](#)) due to limited availability of such treatments, although this may be changing with increased access to psychological therapies through the Improving Access to Psychological Therapies programme (IAPT).² The majority of treatments offered for anxiety disorders are likely to be based in primary care and may involve the GP and/or a

low-intensity psychological therapist such as a primary care mental health worker or the practice counsellor. Self-help bibliotherapy and web-based interventions may be effective for some people with GAD, although referral to secondary care practitioners, such as a high-intensity psychological therapist, may occur for those more severely affected. Referral to secondary care psychiatric mental health services is likely to be rare and reserved for people with the most treatment-resistant symptoms and severe functional impairment.

In summary, there is evidence that GAD is currently significantly under-detected and under-treated in UK primary care settings. This is a potentially serious omission, given the functional impairment and chronicity that can be associated with this diagnosis, particularly when comorbid with depression or physical health problems. There needs to be an increased emphasis on encouraging people to actively present their anxiety symptoms, and for their GPs to be more attuned to this diagnosis (particularly in people known to have depression or a chronic physical health problem) and the need to provide effective evidence-based treatments as early as possible in the course of this disorder before it becomes a long-term problem.

2.4.2. Assessment and co-ordination of care

Primary care and mental health practitioners need to have skills in the identification of GAD and its differentiation from other anxiety and depressive disorders in order to assess GAD and provide appropriate treatment. Assessment involves evaluation of GAD symptoms, especially worry and somatic symptoms of anxiety, the duration of these symptoms, and the extent of the person's functional impairment and distress and their coping resources. Assessment also needs to include evaluation of the symptoms of other anxiety and depressive disorders (especially panic disorder, hypochondriasis, OCD, social phobia, major depressive disorder and dysthymic disorder) given both the overlap of symptoms (for differential diagnosis) and the comorbidity between GAD and these other disorders.

The majority of treatment takes place in primary care or is linked with primary care, usually by either being directly provided by GPs or by psychological practitioners in liaison with GPs. GPs are accordingly central to the coordination of care. Ensuring a clear collaborative treatment plan between GP and psychological practitioners is important. For a small minority of people with very severe disorders, treatment may be provided by a multi-professional team in secondary care with coordination of care through the Care Programme Approach (CPA).

2.4.3. Aims and non-specific effects of treatment and placebo

The aim of treatment for GAD is to relieve symptoms, restore function and prevent relapse. The latter goal is important because GAD manifests as a chronic, relapsing condition and recurrence of illness is common, even when short-term treatment has apparently been successful ([Yonkers et al., 1996](#)). In clinical trials, the outcome of treatment is often determined on standardised rating scales and can be divided into 'response' (where the symptom score has dropped by at least 50%) and 'remission' (almost complete relief of symptoms). In the treatment of depression, remission rather than response is now seen as the preferred goal because people who are essentially asymptomatic have improved functional outcomes and less risk of relapse. It seems probable that similar considerations will apply to the treatment of GAD.

Many people with GAD have had symptoms for long periods of time. Nevertheless, in short-term studies of medication, pill placebo treatment in the context of the clinical care provided by a controlled trial is certainly beneficial for a proportion of people. For example, in a 12-week placebo-controlled trial of escitalopram and paroxetine, just over 40% of participants responded to placebo and about 30% reached remission ([Baldwin et al., 2006](#)). In contrast, naturalistic follow-up studies of people with GAD in the community have found considerably lower remission rates than this, at about 15% a year ([Yonkers et al., 1996](#)). This suggests that either GAD, despite its chronicity, can respond well to pill placebo and non-specific aspects of good clinical management, or that the people who participate in placebo-controlled trials are not typical of the broad range of people with GAD in the

community. In addition, it is not known whether people who respond to a placebo in the short-term will maintain this level of improvement whereas there is some evidence that continuing drug treatment that proved effective in the short-term can help prevent relapse ([Baldwin et al., 2005](#)).

Non-specific effects of treatment are also important in assessing the benefits of psychological therapies such as CBT and applied relaxation. Often such treatments are assessed against 'waitlist' or 'treatment as usual' control groups, which means that the non-specific effects of factors such as increased professional support and instillation of hope will augment the specific effects of a particular therapy. Thus a meta-analysis showed that while CBT was superior to waitlist control in the treatment of GAD, its superiority to supportive psychological therapy could not be clearly demonstrated ([Hunot et al., 2007](#)).

Consistent with this, a substantial number of other approaches have been employed to help people with anxiety disorders, such as exercise, prayer and homeopathic and herbal remedies ([Jorm et al., 2004](#)). This suggests that numerous non-medical approaches, provided they carry meaning and hope for the person concerned, can enable individuals to use their own coping and healing capacities to overcome anxiety symptoms. At present it is not possible to identify those people who will respond to non-specific, as opposed to specific, pharmacological and psychological treatments. In the treatment of depression it appears that the response to placebo lessens as the condition becomes symptomatically more severe ([Khan et al., 2005](#)); this means that the specific benefits of antidepressants are greater in the most severely ill people. Whether the same is true in people with GAD is not clear.

2.4.4. Pharmacological treatments

Placebo-controlled trials indicate that a wide range of medicines with differing pharmacological properties can be effective in the treatment of GAD ([Baldwin et al., 2005](#)). Traditionally, benzodiazepine drugs, such as diazepam, were employed for this purpose but it became clear that their use was commonly associated with the development of tolerance and dependence ([Royal College of Psychiatrists, 2005](#)). For this reason they are now recommended only for short-term use (2 to 4 weeks). Another drug specifically licensed for the treatment of GAD is buspirone, which acts on a particular subtype of serotonin receptor. However, like benzodiazepines, buspirone is recommended for short-term use only ([British Medical Association & the Royal Pharmaceutical Society of Great Britain, 2009](#)).

In recent years antidepressants such as SSRIs have been increasingly used to treat GAD ([Baldwin et al., 2005](#)). Unlike benzodiazepines, antidepressants do not relieve anxiety from the beginning of treatment and a period of some weeks often needs to elapse before significant clinical improvement is seen. Tolerance and dependence do not seem to be a problem with antidepressant treatment, though it should be noted that, like benzodiazepines, antidepressants can cause discontinuation symptoms on abrupt withdrawal ([MHRA, 2004](#)). As well as SSRIs, serotonin noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, are also effective in GAD, as are the older and less selective tricyclic antidepressants (TCAs), such as imipramine. However, TCAs are not as well tolerated as newer antidepressant agents and are more dangerous in overdose ([Baldwin et al., 2005](#)).

In addition to the antidepressants, other compounds also have efficacy in the treatment of GAD. These include the antihistamine hydroxyzine, and the anticonvulsant drug pregabalin, which binds to a subtype of calcium channel in the brain ([Baldwin et al., 2005](#)). Both conventional antipsychotic drugs and the newer 'atypical' antipsychotic agents have also been used in the treatment in GAD, both as a sole therapy and as an 'add-on' to SSRI therapy when the latter has proved ineffective ([Pies, 2009](#)). However, the greater side-effect burden of antipsychotic drugs means that their use is currently restricted to people with refractory conditions, with prescribing guided by secondary care.

While many drug treatments have been demonstrated to be effective in GAD relative to placebo, there are very few comparative studies between active

pharmacological agents. In addition there are no reliable clinical or biological predictors of treatment response in individuals. For this reason the selection of pharmacological treatment is usually made on the basis of the side-effect profile and the history of medication response in a particular individual.

2.4.5. Psychological treatments

Developments in psychological treatments for GAD have tended to parallel changes in the conceptualisation and diagnostic criteria for GAD, moving from a more general approach to more specific interventions.

Early psychological treatments for GAD tended to involve non-specific interventions such as supportive psychotherapy and relaxation training. Initial cognitive behavioural packages for the treatment of GAD ([Borkovec & Costello, 1993](#); [Barlow et al., 1992](#)) focused on the treatment of persistent anxious arousal and often included a number of interventions such as applied relaxation, imagery rehearsal (imaginal practice of coping skills in response to anxiety), stimulus control (establishing increased control over worry) and cognitive approaches based on the work of [Beck and colleagues \(1985\)](#).

More recent adaptations of CBT have emphasised the specific role of worry in GAD and have tried to focus treatment more on the processes thought to underlie the disorder. An example of this is CBT targeting the intolerance of uncertainty ([Dugas et al., 2007](#)) or the metacognitive therapy developed by [Wells \(1999\)](#), which emphasises the importance of the beliefs people have about worry and attempts to modify these.

[Borkovec and colleagues \(2002\)](#) have augmented existing CBT protocols with interpersonal/psychodynamic strategies to address problematic relationship patterns often found in people with GAD and the implications of the avoidance theory of worry, suggesting that people with GAD worry in order to avoid experiencing negative emotions.

Other adaptations of CBT have integrated acceptance-based and mindfulness approaches into treatment for GAD, incorporating the acceptance and experience of frequently avoided emotions into treatment protocols ([Orsillo et al., 2003](#)).

2.4.6. Stepped care

Stepped care ([Scogin et al., 2003](#)) is a framework that is increasingly being used in the UK to specify best practice in the design of clinical pathways to care. Stepped care is designed to increase the efficiency of service provision and therefore benefit patient populations. The basic principle is that patients presenting with a common mental health disorder will 'step through' progressive levels of treatment as necessary, with the expectation that many of these patients will recover or improve while undergoing less intensive treatments. The key features of stepped care are that treatments delivered first should be the least restrictive and that the model is self-correcting. The definition of 'least restrictive' may refer to the impact on patients in terms of cost and personal inconvenience, but can also refer to the amount of specialist therapist time required (that is, treatment intensity). High-intensity treatments are reserved for patients who do not benefit from low-intensity treatments, or for those who can be accurately predicted to not benefit from such treatments. 'Self-correcting' in this context means that the decisions about treatment provision and the effects of treatment are monitored systematically, and changes are made ('stepping up') if current treatments are not achieving significant health gain. Thus, stepped care has the potential for deriving the greatest benefit from available therapeutic resources ([Bower & Gilbody, 2005](#)).

Successful implementation of a stepped-care model is crucial for effective implementation of the NICE guidelines ([Lovell & Bee, 2008](#)). There are two conceptualisations of the stepped-care model. The first is a sequential model, where all people move through the steps in a systematic way, regardless of severity, need or choice. All patients initially receive an evidence-based low-intensity treatment and only 'step up' if and when they have not benefited from the low-intensity treatments offered. The second model is a stratified or multiple-access

model, which allows patients to access more intensive treatment initially, without having received less intensive interventions first (Lovell & Richards, 2000). Stratified stepped-care models have been incorporated into previous NICE guidelines, where stratification has been determined by the person's degree of functional impairment (as in the NICE guideline on OCD and body dysmorphic disorder; NICE, 2005b) or severity of the disorder (as in the NICE guidelines on depression; NICE, 2009b; 2009c).

2.4.7. The economic cost of anxiety disorders – focus on generalised anxiety disorder

Anxiety disorders place a significant burden on individuals as well as on the health-care system. Andlin-Sobocki and colleagues (2005) estimated the cost of anxiety disorders in Europe using published epidemiological and economic data from 28 European countries. Data on healthcare resource utilisation (medication, hospitalisation and outpatient care) and productivity losses due to sick leave associated with anxiety disorders were based on a German national health survey. The estimated total cost of anxiety disorders in Europe was reported to reach €41 billion (2004 prices). The average annual additional cost per person with GAD (relative to a person without an anxiety disorder) was estimated at €1,628 in 2004; of this, 76% was associated with provision of healthcare services and the remaining 24% with productivity losses due to sick leave (Andlin-Sobocki & Wittchen, 2005). The additional per-person cost of GAD was found to be the highest among respective costs of other anxiety disorders, such as panic disorder, agoraphobia, social phobia and OCD.

Only limited data on the healthcare resource utilisation by people with anxiety disorders exist in the UK. According to the Hospital Episode Statistics, in the financial year 2007 to 2008, 8,682 admissions were reported for phobic and other anxiety disorders in England, resulting in 121,359 inpatient bed days; of these, 747 admissions and 16,733 bed days were attributed specifically to GAD (NHS, The Information Centre, 2009). According to the most recent *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009), only 34% of people with GAD were receiving any kind of treatment for their condition at the time of the survey. Of them, 53% were receiving medication, 21% counselling or other psychological therapy, and 26% a combination of drugs and psychological treatment. In addition, 1% of respondents with GAD reported that they had used inpatient services for their condition over the past 3 months, 8% had used outpatient services during the same period, while 25% had used community or day care services during the past year.

A number of studies have estimated the cost of anxiety disorders in the US. DuPont and colleagues (1998) estimated this cost at \$46.6 billion in 1990, which accounted for 31.5% of the total cost of mental disorders in the country. The estimated cost was incurred by healthcare resource utilisation such as mental health services, medication, hospitalisation, nursing homes and outpatient visits (23.1%), productivity losses (76.1%) and, to a lesser extent, by provision of other services such as criminal justice services, incarceration, social welfare administration, as well as family care-giving (0.8%). Greenberg and colleagues (1999) provided a more up-to-date figure of the cost of anxiety disorders in the US, at \$63.1 billion in 1998.

A retrospective, multivariate analysis of data derived from a large claims database in the US demonstrated that people with anxiety disorders are more likely to use outpatient mental health services compared with a control group; they are also more likely to visit medical specialists such as cardiologists and neurologists and to use hospital services, including accident and emergency services. Furthermore, compared with controls, people with anxiety disorders were found to miss more days of work or to have a short-term disability (Marciniak *et al.*, 2004). According to the same analysis, the total medical cost per person with any anxiety disorder was estimated at \$6,475 in 1999 (Marciniak *et al.*, 2005). The multivariate model indicated that, controlling for demographics and other disease states, GAD was associated with an increase of \$2,138 in the total medical cost per person.

An Australian study ([Andrews et al., 2004](#)) estimated the total annual cost of routine treatment for GAD in Australia at AUS\$112.3 million in 1997 prices, based on the results of a national survey of mental health and wellbeing, and an estimated treatment coverage of only 38%. By applying optimal treatment (as achieved by operationalising detailed clinical practice guidelines and expert reviews) and increasing treatment coverage to 70%, the total annual direct medical cost of GAD was expected to rise to AUS\$205.1 million.

Anxiety disorders are associated with a wide range of comorbidities, which result in a substantial increase in total healthcare costs. [Sou tre and colleagues \(1994\)](#) estimated the total direct and indirect costs incurred by people with GAD, with and without comorbidities, using data on 999 people participating in a French cross-sectional study. Controlling for confounding variables, the prevalence of healthcare utilisation in terms of hospitalisation, laboratory tests and medications and the respective medical costs were found to be significantly higher in people with GAD and other comorbidities, as opposed to those with GAD without comorbidities. Moreover, comorbidities were associated with increased absenteeism from work. In particular, comorbid depression ([Marciniak et al., 2005](#); [Wetherell et al., 2007](#); [Zhu et al., 2009](#)) and physical pain ([Olson & Gameroff, 2007](#); [Zhu et al., 2009](#)) have been found to have a significant impact on treatment costs incurred by people with GAD.

Efficient use of available healthcare resources will maximise the health benefits for people with GAD and can potentially reduce costs to the healthcare system and society in the long term.

Footnotes

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Achieving Remission in Generalized Anxiety Disorder

By Laura A. Mandos, PharmD, Jennifer A. Reinhold, PharmD, BCPS, BCPP and Karl Rickels, MD

Feb 2, 2009

Volume: 26

Issue: 2

[Anxiety](#), [Sleep Disorders](#), [Comorbidity In Psychiatry](#), [Generalized Anxiety](#), [Major Depressive Disorder](#)



Generalized anxiety disorder (GAD) is a prevalent, chronic, debilitating mental illness associated with marked impairment in daily functioning.¹ An ongoing evolution of the definition of GAD has resulted in a bifurcation of the historical anxiety neurosis designation.² A diagnosis of GAD currently implies chronic,

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excessive worry lasting at least 6 months and 3 of the possible 6 somatic or psychological symptoms (restlessness, fatigue, muscle tension, irritability, difficulty concentrating, and sleep disturbance).³ GAD typically presents in an episodic pattern of moderate improvement or remission and relapse characterized by a chronic and complicated clinical course.

Chronic worry, a core component of GAD, is consistently found in 10% of the population, and this subset reports a level of anxiety and tension so significant that it markedly impairs daily function. Epidemiological studies, however, suggest a lifetime GAD prevalence of 4% to 7%, a 1-year prevalence of 3% to 5%, and a current prevalence of 1.5% to 3%.⁴ Discrepancies between the incidence of anxiety-related symptoms and potential subsequent underestimation of GAD prevalence may be attributed to DSM-IV diagnostic criterion of 6 months' duration of worry.

It is the robust association of GAD with psychological and physical comorbidities that potentially contributes to the complexity of the illness as well as the limited treatment success.^{4,5} More than 90% of patients with GAD present with an additional psychiatric diagnosis. The ancillary condition is major depressive disorder (MDD) in 48% of patients.^{4,6}

Three primary care studies found that pure GAD, defined as a current episode of GAD in the absence of any other mood, anxiety, or substance use disorder, was associated with meaningful levels of impairment in several life

Strategies for Assessing and Treating Comorbid Panic and Generalized Anxiety Disorder, by Kristalyn Salters-Pedneault, PhD

Can Anticonvulsants Help Patients With Anxiety Disorders? by Marco Mula, MD, PhD

SSRIs as Antihypertensives in Patients With Autonomic Panic Disorder, by Sean Hood, MBBS, MSc

Achieving Remission in Generalized Anxiety Disorder, by Laura A. Mandos, PharmD, Jennifer A. Reinhold, PharmD, and Karl Rickels, MD



Vol 35 No 12

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domains.⁷⁻¹⁰ Ormel and associates⁷

found that the mean numbers of disability days in the past month were much higher among primary care patients with pure GAD than among patients with none of the psychiatric disorders assessed in their survey. The 272 patients with pure GAD had more self-reported dysfunction in occupational role fulfillment and physical disability scores.

Remission/treatment goals

Traditionally, the goal of therapy has been to treat patients with GAD until a response is achieved. The response is either a clinically meaningful improvement in symptoms or a specific magnitude of change in a rating scale score from baseline. Given the extensive use of health care resources, the residual subsyndromal symptoms, and the substantial relapse rate of anxious patients, the goal of therapy has evolved to that of achieving remission.¹¹

Remission is a dichotomous concept in that it is an absence or near absence of symptoms in addition to a return to premorbid functionality.^{11,12} Between 50% and 60% of patients respond clinically to therapy, but only one-third to one-half attain remission or realize full recovery during the acute phase of treatment.¹³ Some patients may achieve “durable remission” within the first 4 to 8 weeks of therapy, which may indicate an eventual sustained remission (lasting 4 to 9 months after acute treatment).¹² Patients who achieve a sustained remission are less likely to experience relapse.¹⁴

Response to treatment and attainment of remission is comprehensively quantified both globally and specifically. The magnitude of treatment outcome is primarily measured by changes in the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global Impression/Improvement (CGI-I) scale, and the total Sheehan Disability Scale (SDS). This multidimensional approach assesses disease-specific anxiety symptoms, quality of life, functioning, and nonspecific symptoms (avoidance).¹² Response generally is defined as at least a 50% reduction in HAM-A score from

baseline, and a “much improved” or “very much improved” rating on the CGI-I.^{11,12,15,16}

Remission is defined as a HAM-A score of 7 or less, with global recovery achieved at a CGI-I score of 1 (“not ill at all” or “borderline mentally ill”), and functional recovery at an SDS score of 5 or less.¹⁴ For this designation of remission to be clinically meaningful, it must incorporate a time component. Remission is not static but rather should be sustainable over a considerable time—at least 8 consecutive weeks.¹⁷

Treatment options

The treatment of GAD involves a sequential process of first resolving the acute, symptomatic anxiety and then maintaining a longer-term constant suppression of chronic anxiety. Historically, benzodiazepines were the mainstay of GAD treatment, although the appropriateness of their use for long-term therapy is now under scrutiny.

Benzodiazepines indirectly affect the release and reuptake of monoamines via enhancement of the inhibitory effects of g-aminobutyric acid, thereby modulating fear, stress, and anxiety responses.¹⁸ Benzodiazepines are indicated for the short-term management of the acute phase of anxiety (2 to 4 weeks) as well as any subsequent exacerbations of anxiety during stable treatment. Their rapid onset and tolerability make them conducive to alleviating anxious symptoms when immediate anxiolytic effects are desired.^{19,20}

A randomized, double-blind study compared response rates among patients treated with imipramine, trazodone, and diazepam. Patients in the diazepam arm had the most significant improvement in anxiety ratings within the first 2 weeks. Within this group, 66% of patients completing the study reported moderate to marked global improvement.²¹ Although more marked improvement was realized in the first 2 weeks of treatment with benzodiazepines, antidepressants consistently afforded the same efficacy as benzodiazepines or even surpassed them after 6 to 12 weeks of treatment, particularly in alleviating psychic symptoms.^{21,22}

Aside from the obvious issue of potential dependence with prolonged use, benzodiazepines are not desirable as first-line therapy because of their potential for withdrawal syndromes and rebound effects on abrupt discontinuation.^{6,23,24} Yet, primary care providers have traditionally used benzodiazepines as first-line treatment of acute anxiety.²⁰

The anxiolytic buspirone has been used with moderate success but has not consistently demonstrated utility in any of the potentially comorbid conditions that can accompany GAD, with the exception of MDD.^{25,26} A retrospective analysis demonstrated significant improvement in HAM-A and global improvement scores relative to baseline, and another study reported buspirone's failure to differ from placebo on numerous outcome measures.^{22,27,28} In addition, buspirone was shown to be superior to placebo in improving anxiety symptoms as well as coexisting depressive symptoms in patients with GAD. The significant anxiolytic effect resulted in more than a 50% response rate, based on reductions in the HAM-A score.²⁹

Buspirone exerts its effect by reducing serotonin (5-HT) release as a partial agonist at 5-HT_{1A} receptors in the hippocampus and as a full agonist at the presynaptic serotonergic auto-receptors.^{14,30} It has been shown to have comparable but slightly weaker efficacy than diazepam, clorazepate, lorazepam, and alprazolam and a slower onset of action.⁶ Its utility is mainly associated with its propensity to relieve the cognitive aspects, but it lacks long-term efficacy, particularly in managing the behavioral and somatic manifestations.¹⁴ In addition, patients who had been previously treated with benzodiazepines, especially recently, tend to have a muted response to buspirone (ie, a reduction in the anxiolytic effects).³¹

Tricyclic antidepressants (TCAs), such as imipramine, are typically more effective at attenuating the psychological symptoms of GAD as opposed to the somatic symptoms. Their inhibition of 5-HT and norepinephrine reuptake produces anxiolytic and antidepressant effects. According to a study conducted by Rickels and colleagues,²¹ significant resolution of anxiety was achieved in

patients who took imipramine between weeks 2 and 8 of therapy, and it afforded effects slightly superior to those of trazodone. Psychic symptoms of tension, apprehension, and worry were most effectively reduced in the imipramine arm: 73% of patients achieved moderate to marked improvement.²¹

The SSRIs are generally regarded as first-line medications, according to domestic and international practice guidelines.^{18,32} Paroxetine, specifically, is FDA-approved for the long-term treatment of depression as well as for GAD at dosages of 20 to 50 mg daily. While the 2- to 4-week delay in onset of therapeutic effect may be discouraging, significant reductions in “anxious mood” have been documented as early as 1 week into treatment.

Remission rates in paroxetine responders at 32 weeks, admittedly a selected population of patients who persevere with treatment, are as high as 73%; relapse rates are only 11%. SSRIs have a sustained therapeutic effect and afford additional incremental improvement over a 24-week period.^{14,33} An 8-week, double-blind, placebo-controlled study examined paroxetine’s impact on HAM-A and SDS scores relative to baseline. The groups that received 20 mg and 40 mg of paroxetine demonstrated a statistically and clinically significant change in the HAM-A and psychic anxiety subscale relative to placebo.

In the intent-to-treat group, 62% in the 20-mg arm and 68% in the 40-mg arm met the criteria for response by week 8 ($P < .001$). Response rates were as high as 80% among patients who completed the study. Remission was achieved in 36% of the patients in the 20-mg group and 42% of the patients in the 40-mg group by week 8 ($P = .004$).²²

An SSRI discontinuation syndrome, characterized by dizziness, insomnia, and flu-like symptoms, occurs in approximately 5% of patients on abrupt discontinuation or significant dose reduction.³² This typically manifests within 1 to 7 days of discontinuation in patients who have been taking an

SSRI for at least 1 month.³⁴ Of the SSRIs, paroxetine is most often implicated in withdrawal symptoms: about 35% to 50% of patients experience discontinuation symptoms on abrupt cessation.³⁵ Reinstating the drug resolves symptoms of withdrawal relatively quickly.³⁶ Tapering the SSRI dosage before discontinuation reduces the likelihood of this syndrome.

A promising alternative in first-line treatment in GAD therapy are the serotonin-norepinephrine reuptake inhibitors, which have been studied in both short- and long-term efficacy trials. Venlafaxine XR at a dosage of 75 to 225 mg daily consistently demonstrated superior efficacy versus placebo in improving anxiety symptoms by measure of a reduction in HAM-A total scores.³⁷ The added benefit of venlafaxine's efficacy in treating symptoms of anxiety in patients with comorbid anxiety and depression, in addition to pure GAD, has elevated its status in the treatment algorithm. Response rates approach 70%, and remission rates are as high as 43% short-term and as high as 61% long-term.^{14,38}

The comorbidity of nonspecific somatic pain complaints is common in patients with GAD, which translates into a compounded negative impact on quality of life. A majority of patients (60%) with GAD and concomitant pain report that they experience a moderate to severe change in their somatic symptoms on days when they feel more anxious or depressed.³⁹ Previous use of benzodiazepines was shown to reduce the probability of a response to venlafaxine in a study by Pollack and colleagues,⁴⁰ although there was no substantial impact on attaining long-term remission.

Abrupt discontinuation of venlafaxine also precipitates a discontinuation syndrome with similar or greater frequency than does paroxetine.³⁵ In addition, more diligent patient monitoring is required secondary to its propensity to precipitate hypertension.³²

Duloxetine is indicated for the treatment of anxiety disorders, MDD, neuropathic pain, and fibromyalgia. Its dual impact on anxious symptoms and somatic pain resulted in 53% to 61% of treated patients who achieved a HAM-A score of 7 or less (symptomatic remission) and an about 47% who achieved an SDS score of 5 or less (functional remission).^{1,41} There is a positive correlation between improvement in pain scores and reduction in SDS scores: most patients who achieved remission also reported greater improvements in visual analog pain scales.³⁹ Venlafaxine or an SSRI have been successfully used as initial monotherapy and long-term therapy; both have been shown to be equally effective.³²

Patients with GAD are considerably more intolerant of normal uncertainty, which results in the formation of negative beliefs about uncertainty.⁴² Thus, these patients could benefit from psychosocial therapy. Numerous psychosocial treatment options are available as monotherapy or as adjunctive therapy in combination with a pharmacological agent. A psychosocial therapy that specifically addresses these cognitive aspects and trains patients to develop and apply coping skills that address psychological and somatic symptoms may be useful.^{43,44}

Overcoming the barriers to remission

A multitude of factors are responsible for worsened outcomes and reduced probability of achieving remission in patients with GAD. Stressful life events, anxiety sensitivity, negative affect, gender, subsyndromal symptoms, and comorbidities all have a palpable impact on the course of illness and outcome. Frequently, patients elect to not complete long-term treatment and thus, life stressors may perpetuate subsyndromal symptoms. Although GAD is characterized by alternating periods of quiescence and exacerbation, the presence of comorbid depression, panic, or any Axis I or Axis II disorder, and a higher initial symptom rating, greatly lessens the possibility of remission.⁴⁵⁻⁴⁷ Pollack and colleagues⁴⁰ found that restlessness predicted a worse treatment outcome, while sleep disturbance was typically associated with a more optimistic outcome.

Most patients who present with GAD have been ill for an average of 15 years before seeking help. As evidenced consistently by the literature, patients with GAD may decide to discontinue medication once they experience some improvement of symptoms.¹⁵ Unfortunately, once they respond positively to treatment, many patients will settle for that level of response instead of continuing therapy. This decision typically arises from fear of dependence on medication.¹⁵ Discontinuation of medication may briefly elicit a mild improvement, secondary to the psychological empowerment of self-management, but it will frequently lead to relapse.⁴⁵ This drives the need for extensive patient education and clear, focused, patient-physician interactions.

Symptomatic remission traditionally precedes functional remission. Patient awareness of this fact should stem the inclination to discontinue therapy prematurely. Most of the first-line, long-term pharmacotherapies for GAD take 2 or more weeks to exert a full pharmacodynamic effect. The interval between the initial prescription of medication and a realization of effect may discourage adherence at an early stage. The likelihood of adherence can be increased by educating the patient about the expected onset of action and by prescribing a benzodiazepine at the start of long-term therapy.⁴⁸

The majority of patients with GAD present to their primary care physician with a somatic complaint that is seemingly unrelated to GAD. This “masquerading” is another potential barrier to treatment.⁴ The inadvertent misdiagnosis of GAD or failure to identify a comorbid disorder results in poor treatment outcomes. Patients who are adherent and do not respond partially or fully to an appropriate medication may need to be reevaluated by a psychiatrist. Reevaluation may well lead to an alternative diagnosis and treatment regimen. Patients who present with predominantly depressive symptoms may be inaccurately labeled as depressed and treated accordingly. Treatment of depressive symptoms alone will not attenuate the somatic or functional aspects of GAD.⁴⁹

Owing to the cyclical pattern of exacerbation and quiescence, many patients present for care during episodic exacerbations when symptoms are most debilitating. The risk is that the perceived acute anxiety will be treated as such, and the underlying, chronic anxiety will not be appropriately resolved.³⁸ Inappropriate resolution of the chronic component of GAD will functionally impede remission and the prevention of relapse. Chronic pharmacotherapeutic treatment, as in MDD, is indicated for most patients who have GAD.

Whether early symptomatic improvement is a potential predictor of future response is currently being explored. A diminution in anxious symptoms within the first 2 weeks of drug therapy may predict remission. Pollack and colleagues¹¹ found that significant improvement by week 2 of treatment translated into an increased likelihood of a clinical HAM-A response and remission of functional disability (SDS). Even moderate symptomatic improvement early on yielded functional remission by the end of week 2.

Conclusions

A constellation of factors influence the likelihood of attaining remission of GAD. The frequent presence of psychiatric or physical comorbidities complicates the clinical picture. Depression is the most prevalent of the psychiatric comorbidities and, as a result, incomplete treatment or misdiagnosis of GAD is often a root cause for treatment failure. Patient nonadherence, high initial symptom ratings, and interpatient variability in clinical presentation of GAD all contribute to the modest remission rates. Perhaps the most consequential factor in determining the propensity for success of GAD treatment is the use of an appropriate drug for an appropriate length of time. The duration of treatment is proportional to the magnitude of the outcome and the potential for realizing symptomatic and functional remission.

While not achievable in all patients, remission is the most appropriate therapeutic goal for GAD. Patients with personality problems and a multitude of comorbidities for whom the illness provides

secondary gain may have difficulty in achieving remission. Although attaining remission is complicated by numerous treatment- and patient-related barriers, overcoming these challenges is feasible in the majority of patients. The diagnosis of GAD must be distinct from any other intervening psychiatric or somatic disorders. While the level of comorbidity is relatively high, the GAD diagnosis must be reliable and not confounded by other disorders. Treatment outcome goals must be clearly established in advance of therapy and should be based on the individual patient's needs.

Psychotropic drug therapy for appropriate treatment duration is the foundation of successful therapy. A single drug is typically initially prescribed for patients who have GAD. Inadequate responses to monotherapy may warrant the addition of a second pharmacological agent or psychotherapy. Augmentation of drug therapy with benzodiazepines for 3 to 4 weeks and then gradually tapering the benzodiazepine may further reduce the reemergence of anxiety symptoms.⁶ Patients who demonstrate incomplete remission or lack of response need to be reevaluated in a timely manner to confirm the GAD diagnosis. In adherent patients for whom an appropriate duration of single drug therapy is unsuccessful, consider augmentation with a benzodiazepine or an anxiolytic with a different mechanism of action. The addition of a psychotherapeutic modality and/or a new pharmacological agent may generate additional benefit. Continuation of pharmacotherapy for 6 to 12 months beyond symptom resolution increases the likelihood of a sustained remission and decreases the likelihood of relapse.

Drugs Mentioned in This Article

Alprazolam (Xanax)

Buspirone (BuSpar)

Clorazepate (ClarazeCaps, others)

Diazepam (Valium)

Duloxetine (Cymbalta)

Imipramine (Tofranil)

Lorazepam (Ativan)

Paroxetine (Paxil)

Trazodone (Desyrel)

Venlafaxine (Effexor)

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Question 4

Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation

Contents

Key Findings – 3

New Evidence –

Cannabidiol in Anxiety and Sleep: A Large Case Series – 6

Use of cannabidiol in anxiety and anxiety-related disorders – 12

Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users – 21

Previously Submitted Evidence –

Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug – 27

The Endocannabinoid System and the Brain – 35

Anxiogenic-like effects of chronic cannabidiol administration in rats – 56

Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow – 67

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders – 78

Cannabidiol as a Potential Treatment for Anxiety Disorders – 96

Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report – 109

Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics – 120

Therapeutic Benefits of Cannabis: A Patient Survey – 130

Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization – 135

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects – 145

Patient-Reported Symptom Relief Following Medical Cannabis Consumption – 168

Key Findings

Marijuana's schedule I status makes studies on its medical use difficult to conduct. Because of this, evidence that medical marijuana is effective in treating generalized anxiety disorder is more limited than that of an FDA approved pharmaceutical, but significant evidence of medical marijuana's effectiveness can still be seen.

New Evidence

Cannabidiol in Anxiety and Sleep: A Large Case Series

CBD appears to be better tolerated than routine psychiatric medications. Furthermore, CBD displays promise as a tool for reducing anxiety in clinical populations.

Use of cannabidiol in anxiety and anxiety-related disorders

CBD has consistently demonstrated acute reduction in anxiety-related symptoms in patients, specifically within GAD and SAD. Additionally, the use of CBD for these disorders has shown increasingly minimal adverse effects compared with existing pharmacotherapy.

Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users

The vast majority of patients perceived symptom improvement with CMP (cannabis for medical purposes) use and did not believe CMP use was associated with impairment or an inability to control use.

Previously Submitted Evidence

Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug

Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD.

The Endocannabinoid System and the Brain

Cannabidiol, which does not bind to either CB1 or CB2, possesses anxiolytic and antipsychotic properties (Mechoulam et al. 2002) both in animals and in humans.

Anxiogenic-like effects of chronic cannabidiol administration in rats

Chronic administration of CBD produced an anxiogenic-like effect in clear opposition to the acute anxiolytic profile previously reported. In addition, CBD decreased the expression of proteins that have been shown to be enhanced by chronic treatment with antidepressant/anxiolytic drugs.

Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow

These results suggest that CBD has anxiolytic properties, and that these effects are mediated by an action on limbic and paralimbic brain areas.

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders

In agreement with the results obtained in animal models, clinical studies confirmed that CBD has anxiolytic properties

Cannabidiol as a Potential Treatment for Anxiety Disorders

Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders...

Cannabis Use in HIV for Pain and Other Medical Symptoms

Relief of symptoms of anxiety and depression was common, as was general symptom relief.

Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report

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 ...

Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics

37.8% of patients in this study reported a benefit of medical marijuana was a reduction in anxiety symptoms.

Therapeutic Benefits of Cannabis: A Patient Survey

Other reported therapeutic benefits [of cannabis] 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.

Therapeutic Benefits of Cannabis: A Patient Survey – Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization

82.9% of patients studied reported relief from anxiety symptoms.

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

The myriad effects of CBD on 5-HT_{1A} activity provide a strong rationale for this and other phytocannabinoids as base compounds for treatment of anxiety

Patient-Reported Symptom Relief Following Medical Cannabis Consumption

The first two regressions shown in Table 2 indicate that people with anxiety and depression report greater relief from using cannabis than people with chronic pain, and users with higher starting symptom levels report greater symptom relief.

Cannabidiol in Anxiety and Sleep: A Large Case Series

Scott Shannon, MD¹; Nicole Lewis, ND²; Heather Lee, PA-C³; Shannon Hughes, PhD⁴

Perm J 2019;23:18-041

E-pub: 01/07/2019

<https://doi.org/10.7812/TPP/18-041>

ABSTRACT

Context: Cannabidiol (CBD) is one of many cannabinoid compounds found in cannabis. It does not appear to alter consciousness or trigger a “high.” A recent surge in scientific publications has found preclinical and clinical evidence documenting value for CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points toward a calming effect for CBD in the central nervous system. Interest in CBD as a treatment of a wide range of disorders has exploded, yet few clinical studies of CBD exist in the psychiatric literature.

Objective: To determine whether CBD helps improve sleep and/or anxiety in a clinical population.

Design: A large retrospective case series at a psychiatric clinic involving clinical application of CBD for anxiety and sleep complaints as an adjunct to usual treatment. The retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients.

Main Outcome Measures: Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment.

Results: The final sample consisted of 72 adults presenting with primary concerns of anxiety (n = 47) or poor sleep (n = 25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all but 3 patients.

Conclusion: Cannabidiol may hold benefit for anxiety-related disorders. Controlled clinical studies are needed.

INTRODUCTION

The *Cannabis* plant has been cultivated and used for its medicinal and industrial benefits dating back to ancient times. *Cannabis sativa* and *Cannabis indica* are the 2 main species.¹ The *Cannabis* plant contains more than 80 different chemicals known as cannabinoids. The most abundant cannabinoid, tetrahydrocannabinol (THC), is well known for its psychoactive properties, whereas cannabidiol (CBD) is the second-most abundant and is nonpsychoactive. Different strains of the plant are grown containing varying amounts of THC and CBD. Hemp plants are grown for their fibers and high levels of CBD that can be extracted to make oil, but marijuana plants grown for recreational use have higher concentrations of THC compared with CBD.² Industrial hemp must contain less than 0.3% THC to be considered legal, and it is from this plant that CBD oil is extracted.³

Many different cultures have used the *Cannabis* plant to treat a plethora of ailments. Practitioners in ancient China targeted malaria, menstrual symptoms, gout, and constipation. During medieval times, cannabis was used for pain, epilepsy, nausea,

and vomiting, and in Western medicine it was commonly used as an analgesic.^{4,5} In the US, physicians prescribed *Cannabis sativa* for a multitude of illnesses until restrictions were put in place in the 1930s and then finally stopped using it in 1970 when the federal government listed marijuana as a Schedule I substance, claiming it an illegal substance with no medical value. California was the first state to go against the federal ban and legalize medical marijuana in 1996.⁶ As of June 2018, 9 states and Washington, DC, have legalized recreational marijuana, and 30 states and Washington, DC, allow for use of medical marijuana.⁷ The purpose of the present study is to describe the effects of CBD on anxiety and sleep among patients in a clinic presenting with anxiety or sleep as a primary concern.

CBD has demonstrated preliminary efficacy for a range of physical and mental health care problems. In the decade before 2012, there were only 9 published studies on the use of cannabinoids for medicinal treatment of pain; since then, 30 articles have been published on this topic, according to a PubMed search conducted in December 2017. Most notable was a study conducted at the University of California, San Diego’s Center for Medicinal Cannabis Research that showed cannabis cigarettes reduced pain by 34% to 40% compared with placebo (17% to 20% decrease in pain).⁸ In particular, CBD appears to hold benefits for a wide range of neurologic disorders, including decreasing major seizures. A recent large, well-controlled study of pediatric epilepsy documented a beneficial effect of CBD in reducing seizure frequency by more than 50%.⁹ In addition to endorphin release, the “runner’s high” experience after exercise has been shown to be induced in part by anandamide acting on CB1 receptors, eliciting anxiolytic effects on the body.¹⁰ The activity of CBD at 5-HT_{1A} receptors may drive its neuroprotective, antidepressive, and anxiolytic benefits, although the mechanism of action by which CBD decreases anxiety is still unclear.¹¹ CBD was shown to be helpful for decreasing anxiety through a simulated public speaking test at doses of 300 mg to 600 mg in single-dose studies.¹²⁻¹⁴ Other studies suggest lower doses of 10 mg/kg having a more anxiolytic effect than higher doses of 100 mg/kg in rats.¹⁵ A crossover study comparing CBD with nitrazepam found that high-dose CBD at 160 mg increased the duration of sleep.¹⁶ Another crossover study showed that

Author Affiliations

¹ Department of Psychiatry, University of Colorado, Denver

² Department of Naturopathic Medicine, Wholeness Center, Fort Collins, CO

³ North Range Behavioral Health, Greeley, CO

⁴ School of Social Work, Colorado State University College of Health and Human Sciences, Fort Collins

Corresponding Author

Scott Shannon, MD (scottshannon@cowisp.net)

Keywords: anxiety, cannabidiol, CBD, sleep

plasma cortisol levels decreased more significantly when given oral CBD, 300 to 600 mg, but these patients experienced a sedative effect.¹⁷ The higher doses of CBD that studies suggest are therapeutic for anxiety, insomnia, and epilepsy may also increase mental sedation.¹⁶ Administration of CBD via different routes and long-term use of 10 mg/d to 400 mg/d did not create a toxic effect on patients. Doses up to 1500 mg/d have been well tolerated in the literature.¹⁸ Most of the research done has been in animal models and has shown potential benefit, but clinical data from randomized controlled experiments remain limited.

Finally, the most notable benefit of cannabis as a form of treatment is safety. There have been no reports of lethal overdose with either of the cannabinoids and, outside of concerns over abuse, major complications are very limited.¹⁹ Current research indicates that cannabis has a low overall risk with short-term use, but more research is needed to clarify possible long-term risks and harms.

Given the promising biochemical, physiologic, and preclinical data on CBD, a remarkable lack of randomized clinical trials and other formal clinical studies exist in the psychiatric arena. The present study describes a series of patients using CBD for treatment of anxiety or sleep disturbances in a clinical practice setting. Given the paucity of data in this area, clinical observations can be quite useful to advance the knowledge base and to offer questions for further investigation. This study aimed to determine whether CBD is helpful for improving sleep and/or anxiety in a clinical population. Given the novel nature of this treatment, our study also focused on tolerability and safety concerns. As a part of the evolving legal status of cannabis, our investigation also looked at patient acceptance.

METHODS

Design and Procedures

A retrospective chart review was conducted of adult psychiatric patients treated with CBD for anxiety or sleep as an adjunct to treatment as usual at a large psychiatric outpatient clinic. Any current psychiatric patient with a diagnosis by a mental health professional (psychiatrist, psychiatric nurse practitioner, or physician assistant) of a sleep or anxiety disorder was considered. Diagnosis was made by clinical evaluation followed by baseline psychologic measures. These measures were repeated monthly. Comorbid psychiatric illnesses were not a basis for exclusion. Accordingly, other psychiatric medications were administered as per routine patient care. Selection for the case series was contingent on informed consent to be treated with CBD for 1 of these 2 disorders and at least 1 month of active treatment with CBD. Patients treated with CBD were provided with psychiatric care and medications as usual. Most patients continued to receive their psychiatric medications. The patient population mirrored the clinic population at large with the exception that it was younger.

Nearly all patients were given CBD 25 mg/d in capsule form. If anxiety complaints predominated, the dosing was every morning, after breakfast. If sleep complaints predominated, the dosing was every evening, after dinner. A handful of patients were given CBD 50 mg/d or 75 mg/d. One patient with a trauma history

and schizoaffective disorder received a CBD dosage that was gradually increased to 175 mg/d.

Often CBD was employed as a method to avoid or to reduce psychiatric medications. The CBD selection and dosing reflected the individual practitioner's clinical preference. Informed consent was obtained for each patient who was treated and considered for this study. Monthly visits included clinical evaluation and documentation of patients' anxiety and sleep status using validated measures. CBD was added to care, dropped from care, or refused as per individual patient and practitioner preference. The Western Institutional Review Board, Puyallup, WA, approved this retrospective chart review.

Setting and Sample

Wholeness Center is a large mental health clinic in Fort Collins, CO, that focuses on integrative medicine and psychiatry. Practitioners from a range of disciplines (psychiatry, naturopathy, acupuncture, neurofeedback, yoga, etc) work together in a collaborative and cross-disciplinary environment. CBD had been widely incorporated into clinical care at Wholeness Center a few years before this study, on the basis of existing research and patient experience.

The sampling frame consisted of 103 adult patients who were consecutively treated with CBD at our psychiatric outpatient clinic. Eighty-two (79.6%) of the 103 adult patients had a documented anxiety or sleep disorder diagnosis. Patients with sole or primary diagnoses of schizophrenia, posttraumatic stress disorder, and agitated depression were excluded. Ten patients were further excluded because they had only 1 documented visit, with no follow-up assessment. The final sample consisted of 72 adult patients presenting with primary concerns of anxiety (65.3%; $n = 47$) or poor sleep (34.7%; $n = 25$) and who had at least 1 follow-up visit after CBD was prescribed.

Main Outcome Measures

Sleep and anxiety were the targets of this descriptive report. Sleep concerns were tracked at monthly visits using the Pittsburgh Sleep Quality Index. Anxiety levels were monitored at monthly visits using the Hamilton Anxiety Rating Scale. Both scales are nonproprietary. The Hamilton Anxiety Rating Scale is a widely used and validated anxiety measure with 14 individual questions. It was first used in 1959 and covers a wide range of anxiety-related concerns. The score ranges from 0 to 56. A score under 17 indicates mild anxiety, and a score above 25 indicates severe anxiety. The Pittsburgh Sleep Quality Index is a self-report measure that assesses the quality of sleep during a 1-month period. It consists of 19 items that have been found to be reliable and valid in the assessment of a range of sleep-related problems. Each item is rated 0 to 3 and yields a total score from 0 to 21. A higher number indicates more sleep-related concerns. A score of 5 or greater indicates a "poor sleeper."

Side effects and tolerability of CBD treatment were assessed through spontaneous patient self-reports and were documented in case records. Any other spontaneous comments or complaints of patients were also documented in case records and included in this analysis.

Data Analysis

Deidentified patient data were evaluated using descriptive statistics and plotted graphically for visual analysis and interpretation of trends.

RESULTS

The average age for patients with anxiety was 34 years (range = 18-70 years) and age 36.5 years for patients with sleep disorders (range = 18-72 years). Most patients with an anxiety diagnosis were men (59.6%, 28/47), whereas more sleep-disordered patients were women (64.0%, 16/25). All 72 patients completed sleep and anxiety assessments at the onset of CBD treatment and at the first monthly follow-up. By the second monthly follow-up, 41 patients (56.9%) remained on CBD treatment and completed assessments; 27 patients (37.5%) remained on CBD treatment at the third monthly assessment.

Table 1 provides means and standard deviations for sleep and anxiety scores at baseline and during the follow-up period for adults taking CBD. Figure 1 graphically displays the trend in anxiety and sleep scores over the study period. On average, anxiety and sleep improved for most patients, and these improvements were sustained over time. At the first monthly assessment after the start of CBD treatment, 79.2% (57/72) and 66.7% (48/72) of all patients experienced an improvement in anxiety and sleep, respectively; 15.3% (11/72) and 25.0% (18/72) experienced worsening symptoms in anxiety and sleep, respectively. Two months after the start of CBD treatment, 78.1% (32/41) and 56.1% (23/41) of patients reported improvement in anxiety and sleep, respectively, compared with the prior monthly visit; again, 19.5% (8/41) and 26.8% (11/41), respectively, reported worsening problems as compared with the prior month.

These results demonstrated a more sustained response to anxiety than for sleep over time. Patient records displayed a larger decrease in anxiety scores than in sleep scores. The sleep scores demonstrated mild improvement. The anxiety scores decreased within the first month and then remained decreased during the study duration.

Parameter	HAM-A, mean (SD)	PSQI, mean (SD)
Anxiety (n = 47)		
Baseline	23.87 (9.87)	10.98 (3.43)
1-month follow-up	18.02 (7.56)	8.88 (3.68)
2-month follow-up	16.35 (8.80)	8.59 (2.91)
3-month follow-up	16.36 (9.80)	9.25 (2.46)
Sleep disorder (n = 25)		
Baseline	22.18 (7.55)	13.08 (3.03)
1-month follow-up	17.82 (9.72)	10.64 (3.89)
2-month follow-up	17.36 (10.91)	9.39 (3.81)
3-month follow-up	13.78 (7.86)	9.33 (4.63)

HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation.

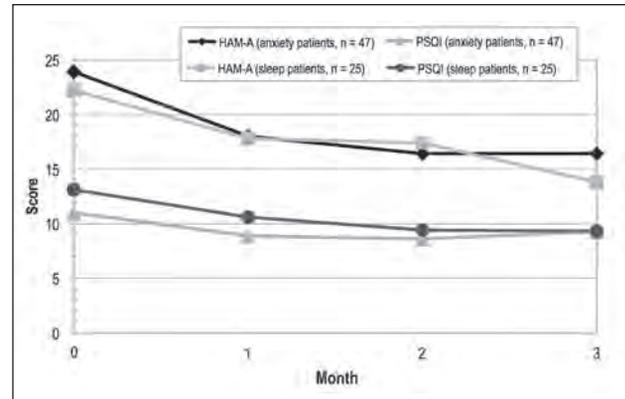


Figure 1. Mean anxiety and sleep scores for adults using cannabidiol treatment. HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburgh Sleep Quality Index.

CBD was well tolerated, with few patients reporting side effects. Two patients discontinued treatment within the first week because of fatigue. Three patients noted mild sedation initially that appeared to abate in the first few weeks. One patient with a developmental disorder (aged 21 years) had to be taken off the CBD regimen because of increased sexually inappropriate behavior. The CBD was held, and the behavior disappeared. The behavior reappeared on redosing 2 weeks later, and the CBD regimen was formally discontinued. The treating psychiatrist thought this was related to disinhibition because the patient's anxiety responded dramatically. One patient noted dry eyes. Reasons for patients not following-up at later assessment points are largely unknown but are probably because of standard attrition experienced in usual clinical practice. There was no evidence to suggest patients discontinued care because of tolerability concerns. The attrition rates were similar in nature and size to those found in routinely scheduled visits in this clinic.

The treatment with CBD was in general well accepted, as judged by the clinicians' and patients' responses. Four patients declined CBD treatment because of religious or ethical concerns about the relation to cannabis. Nearly all patients easily provided informed consent once the nature of the treatment was explained. Most patients appreciated the opportunity to try something natural and avoid further or initial psychiatric medication use.

DISCUSSION

In an outpatient psychiatric population, sleep scores displayed no sustained improvements during the 3-month study. Anxiety scores decreased fairly rapidly, and this decrease was sustained during the study period. These results are consistent with the existing preclinical and clinical data on CBD. CBD was well accepted and well tolerated in our patients. Side effects were minimal (mainly fatigue) and may be related to dosing.

The doses used in this study (25 mg/d to 175 mg/d) were much lower than those reported in some of the clinical literature (300 mg/d to 600 mg/d)^{12-14,17} for 2 reasons. The first is that in our experience lower doses appear to elicit an adequate clinical

response. Second, the current retail cost of CBD would make the use of 600 mg/d cost prohibitive.

Study Limitations

These results must be interpreted cautiously because this was a naturalistic study, all patients were receiving open-label treatment, and there was no comparison group. Concurrent psychiatric medications were employed as in routine clinical care. This is both a limitation and strength, as very few publications exist in this population. Other researchers have noted that the large societal notoriety about cannabis and medical marijuana probably contributes to a larger-than-normal placebo effect.²⁰ Any study that explores efficacy in this therapy probably will struggle with a potentially inflated placebo effect that will make these determinations more difficult. Likewise, the clinical population in this case series is skewed younger than typical for our clinic, and future studies could explore the possible selection bias inherent in this treatment option. Most patients were also taking psychiatric medications and receiving other mental health services, such as counseling, which limits the ability to make any causal links to CBD treatment. Clinical attrition is evident in the dataset. The reason for this might be related to CBD ingestion or not, so the overall component remains unclear. Furthermore, patients at our clinic often express a desire to reduce or to avoid use of psychiatric medications, which may contribute to an enhanced placebo effect or additional bias. The length of clinical monitoring may help to decrease this concern. However, the clinical data in this analysis show a trend toward clinically significant relief of anxiety upon the start of CBD treatment.

Legality of Cannabidiol

The legality of CBD is not clear. Like the issues surrounding the legality of cannabis in general, CBD presents the clinician with a confusing state vs federal legal quandary, and this keeps the issue in question. CBD is legal in the 33 states that have legalized medical or recreational use of marijuana and in 17 other states that have legalized some form of CBD, according to the National Organization for the Reform of Marijuana Laws (NORML).²¹ But like marijuana, it is still not legal at the federal level. The federal government has announced that it is not focused on this compound in terms of enforcement or interdiction.²² However, CBD is interpreted by the Drug Enforcement Administration, Food and Drug Administration, and Congress to be a Schedule I substance, and therefore it is illegal in all 50 states.²³ Pragmatically, CBD is widely available on the Internet, with sales expected to reach \$1 billion by 2020. Pending federal legislation to redefine the legal status of cannabis would clarify this complex issue. Canada's move to legalize cannabis in October 2018 further highlights the need for a speedy resolution to this question.²⁴

CONCLUSION

Formal studies on efficacy and dose finding are much needed. Some urgency exists, given the explosion of lay interest in this topic and the rush to market these compounds. Current

understanding of the physiology and neurologic pathways points to a benefit with anxiety-related issues. The results of our clinical report support the existing scientific evidence. In our study, we saw no evidence of a safety issue that would limit future studies. In this evaluation, CBD appears to be better tolerated than routine psychiatric medications. Furthermore, CBD displays promise as a tool for reducing anxiety in clinical populations, but given the open-label and nonrandomized nature of this large case series, all results must be interpreted very cautiously. Randomized and controlled trials are needed to provide definitive clinical guidance. ❖

Disclosure Statement

Dr Shannon has published several professional books on integrative mental health. Dr Shannon is a Principal Investigator for a Phase 3 study of 3,4-methylenedioxy-methamphetamine (MDMA)-assisted psychotherapy for severe posttraumatic stress disorder and receives compensation for his clinical work from the Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA. The other authors have no conflicts of interests to disclose.

Acknowledgments

CV Sciences Inc, Las Vegas, NV, provided cannabidiol products for the study. CV Sciences was not involved in the data collection, data interpretation, preparation of the report, or decision to submit the report for publication. No other financial support was provided. The authors would like to express their deep appreciation to the staff and clinicians at Wholeness Center for their professionalism.

Kathleen Loudon, ELS, of Loudon Health Communications provided editorial assistance.

How to Cite this Article

Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in anxiety and sleep: A large case series. *Perm J* 2019;23:18-041. DOI: <https://doi.org/10.7812/TPP/18-041>

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Contents lists available at ScienceDirect

Journal of the American Pharmacists Association

journal homepage: www.japha.org

REVIEW

Use of cannabidiol in anxiety and anxiety-related disorders

Jessica W. Skelley*, Crystal M. Deas, Zachary Curren, Jonathan Ennis

ARTICLE INFO

Article history:

Received 31 July 2019

Accepted 8 November 2019

ABSTRACT

Objective: Cannabidiol (CBD) has a proposed novel role in the management of anxiety owing to its actions on the endocannabinoid system. The purpose of this systematic review was to evaluate the current evidence on the safety and efficacy of CBD in anxiety and anxiety-related disorders.

Data sources: A literature search was conducted on PubMed, Google Scholar, and International Pharmaceutical Abstracts from database inception through June 2019. A bibliographic search of relevant articles was also conducted.

Study selection: Articles published from case reports, case series, or randomized controlled trials on human subjects were included in the review if they examined the safety and efficacy of CBD therapy in anxiety and anxiety-related disorders.

Data extraction: Two reviewers independently extracted the following data from the articles: year of publication; study design; patient characteristics (sex; type of anxiety disorder; use of concomitant anxiolytic therapy); dosing strategy and route of CBD administration; and safety and efficacy outcomes.

Results: Eight articles were included in the review: 6 small, randomized controlled trials; 1 case series; and 1 case report. These studies examined the role of CBD in the anxiety response of healthy volunteers; in generalized anxiety disorder; in social anxiety disorder; and in the anxiety component of posttraumatic stress syndrome. No articles that evaluated CBD in panic disorder, specific phobia, separation anxiety, and obsessive-compulsive disorder were identified. In the studies, CBD was administered orally as a capsule or as a sublingual spray and as either monotherapy or adjunctive therapy. Doses varied widely, with studies employing fixed CBD doses ranging from 6 mg to 400 mg per dose. Various anxiety assessment scales were used in the studies to assess efficacy, with CBD demonstrating improved clinical outcomes among the instruments. In general, CBD was well-tolerated and associated with minimal adverse effects, with the most commonly noted adverse effects being fatigue and sedation.

Conclusion: CBD has a promising role as alternative therapy in the management of anxiety disorders. However, more studies with standardized approaches to dosing and clinical outcome measurements are needed to determine the appropriate dosing strategy for CBD and its place in therapy.

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Background

Anxiety is an adaptive, emotional response that naturally occurs as a result of a perceived threat.¹ Anxiety becomes maladaptive when it occurs excessively or inappropriately in the absence of relevant threatening stimuli.¹ The exact pathophysiology of anxiety-related disorders is unknown.

Disclosure: The authors declare no relevant conflicts of interest or financial relationships.

* **Correspondence:** Jessica W. Skelley, PharmD, BCACP, Associate Professor of Pharmacy Practice, McWhorter School of Pharmacy, Samford University, 800 Lakeshore Dr, Birmingham, AL 35229.

E-mail address: jmwhalen@samford.edu (J.W. Skelley).

However, results from neuroimaging and biochemical studies suggest that the variation between adaptive and maladaptive anxiety responses is modulated by regions of the limbic system—primarily the amygdala—and key neurotransmitters, such as dopamine (DA), norepinephrine (NE), γ -aminobutyric acid (GABA), and serotonin (5-HT).²

Within *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), specific phobia (SP), and separation anxiety are classified as anxiety disorders. Obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) share a common symptomatology of excessive anxiety; however, they are reviewed in their own respective chapters within *the DSM-5*, after the

Key Points**Background:**

- As a group, anxiety disorders and anxiety-related disorders are the most common psychiatric conditions in the United States. As such, they pose a serious disease burden to patients and the health care system because of decreased well-being, physical impairment, loss of productivity, and increased health care utilization costs.
- At present, the mainstay agents for treatment of anxiety have limitations in efficacy and are associated with a number of adverse effects, which suggests the need for new pharmacotherapies for these disorders.
- Cannabidiol (CBD) is a nonhallucinogenic chemical compound, derived from the plant *Cannabis sativa*, with a novel role in the management of anxiety.
- This article provides a review of evidence on the clinical efficacy and safety of CBD used to manage anxiety and anxiety-related disorders.

Findings:

- In the studies reviewed, CBD consistently demonstrated improved clinical outcomes in anxiety disorders, with a minimal adverse-effect profile.
- However, optimal dose, route of administration, and dosing strategy (acute vs. chronic use) of CBD in the management of anxiety disorders remain undetermined.
- Pharmacists have an essential role in advising patients and prescribers on the use of alternative therapies. Given the heightened popularity of CBD, it is crucial that pharmacists are knowledgeable about its benefits and are able to provide appropriate recommendations on the place in therapy of CBD in the treatment of common disorders, such as anxiety.

chapter on anxiety disorders. As a group, the anxiety disorders and anxiety-related disorders of PTSD and OCD are the most common psychiatric conditions in the United States.³ Taken together, these disorders have an estimated lifetime prevalence of approximately 29% for U.S. adults.^{3,4} As such, they pose a substantial disease burden to patients and the health care system because of their association with decreased well-being, physical impairment, loss of productivity, and increased health care utilization costs.^{3,4}

At present, the primary pharmacologic treatment for anxiety and anxiety-related disorders involves the use of medications that modulate the activity of DA, NE, GABA, and 5-HT neurotransmitters. Benzodiazepines are prescribed commonly because of their modulation of GABA. Likewise, antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, 5-HT receptor antagonists, monoamine oxidase inhibitors, and buspirone are frequently used for their effects

on DA, NE, and 5-HT. Less commonly prescribed agents for anxiety and anxiety-related disorders include second generation antipsychotics, anticonvulsants, and certain antihistamines, such as hydroxyzine. These pharmacotherapies have limitations in efficacy and are associated with a number of adverse effects (e.g., sexual dysfunction and potential for dependence and tolerance), which suggests the need for novel therapeutic modalities for management of anxiety and anxiety-related disorders.^{5–7}

The endocannabinoid system (ECS) is a promising therapeutic target for anxiolytic-drug development owing to its purported role in modulating synaptic plasticity and neuronal activity involved in the anxiety response.^{4,5,8–12} Primary activity of signaling within the ECS is thought to be because of the action on 2 known cannabinoid receptors, CB1 and CB2.^{4,5,8–12} Cannabidiol (CBD), a chemical compound known as a phytocannabinoid, is derived from the plant *Cannabis sativa* and may have a role in the management of anxiety given its pharmacologic activity within the ECS.^{4,5,8–12} Among the more than 400 chemicals produced by *C sativa*, delta-9-tetrahydrocannabinol (THC) and CBD are the major compounds.^{4,5,8–12} THC is the most abundant psychoactive chemical and is primarily responsible for the well-known hallucinogenic effects of *C sativa*. In contrast, CBD is not psychoactive.^{4,5,8–12}

In the literature, CBD has several proposed therapeutic effects accomplished through multiple mechanisms. Despite low affinity for CB1 and CB2 receptors, CBD has proposed indirect activity on the ECS through its action of inhibiting the inactivation of anandamide—a neurotransmitter within the ECS—which leads to activity on the CB1 receptor.^{4,5,8–12} This mechanism, in conjunction with activity on 5-HT_{1A} receptors, is believed to be a key factor in the reported therapeutic effects of CBD in anxiety.^{4,5,8–12} Available literature suggests a favorable adverse-effect profile of CBD and minimal drug interaction potential when compared with other therapeutic agents; however, it should be noted that there is a dearth of studies examining these parameters.¹³

CBD can be administered through various routes of administration and is currently available and marketed in numerous formulations, such as tinctures administered under the tongue, concentrated oil administered orally or topically, topical compounds such as ointments and creams, vaporized solutions, and infused beverages and food items. In the United States, there is only 1 Food and Drug Administration (FDA)-approved CBD product, Epidiolex, which is approved for treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.¹⁴ All other cannabis-derived CBD products remain under the purview of the FDA regulation under the 2018 Farm Bill, and determination of the scope of this regulation is evolving.¹⁵ With the dramatic increase in use of CBD products, it is prudent to assess the validity of therapeutic claims as well as the safety profile.¹⁵ This information will be beneficial to clinicians when examining the risks and benefits of using CBD for pharmacologic activity in anxiety.

Objective

The purpose of this systematic review was to evaluate the current evidence on the safety and efficacy of CBD in the management of anxiety and anxiety-related disorders.

Methods

Data sources

This study was a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance statement.¹⁶ A free text search of PubMed (January 1996-June 2019) was conducted. The term “cannabidiol” was combined with either “generalized anxiety disorder,” or “social anxiety disorder,” or “panic disorder,” or “specific phobia,” or “separation anxiety,” or “post-traumatic stress disorder,” or “obsessive compulsive disorder” with the Boolean operator AND. This free text search was duplicated on Google Scholar and International Pharmaceutical Abstracts. In addition, references of relevant articles were also reviewed.

Study selection

Articles were included in the review if they examined CBD treatment in diagnosed anxiety or anxiety-related disorders or if they evaluated the anxiety response in healthy volunteers. Animal studies, articles evaluating the psychosis components of PTSD and OCD, and studies evaluating the role of CBD in managing THC-related anxiety were excluded from review. In addition, editorials, commentaries, and letters to the editor

were excluded. Two reviewers independently executed the search and screened articles for inclusion.

Data extraction

Two reviewers independently extracted the following data from the articles: year of publication; study design; patient characteristics (sex; type of anxiety disorder; use of concomitant anxiolytic therapy); dosing strategy and route of CBD administration; and safety and efficacy outcomes. Efficacy outcomes included scores on assessment scales for anxiety, such as the Screen for Anxiety-Related Disorders (SCARED), Hamilton Anxiety Rating Scale (HAM-A), Visual Analogue Mood Scale (VAMS), State-Trait Anxiety Inventory (STAI), Bodily Symptoms Scale (BSS), and Negative Self-Statements subscale (SSPS-N).

Results

Study characteristics

A total of 233 potentially relevant articles resulted from the search. Eight articles met criteria for full text review: 6 small, randomized controlled trials; 1 case series; and 1 case report (Figure 1). One article evaluating the role of CBD in the anxiety response of healthy volunteers, 1 assessing CBD in GAD, 1

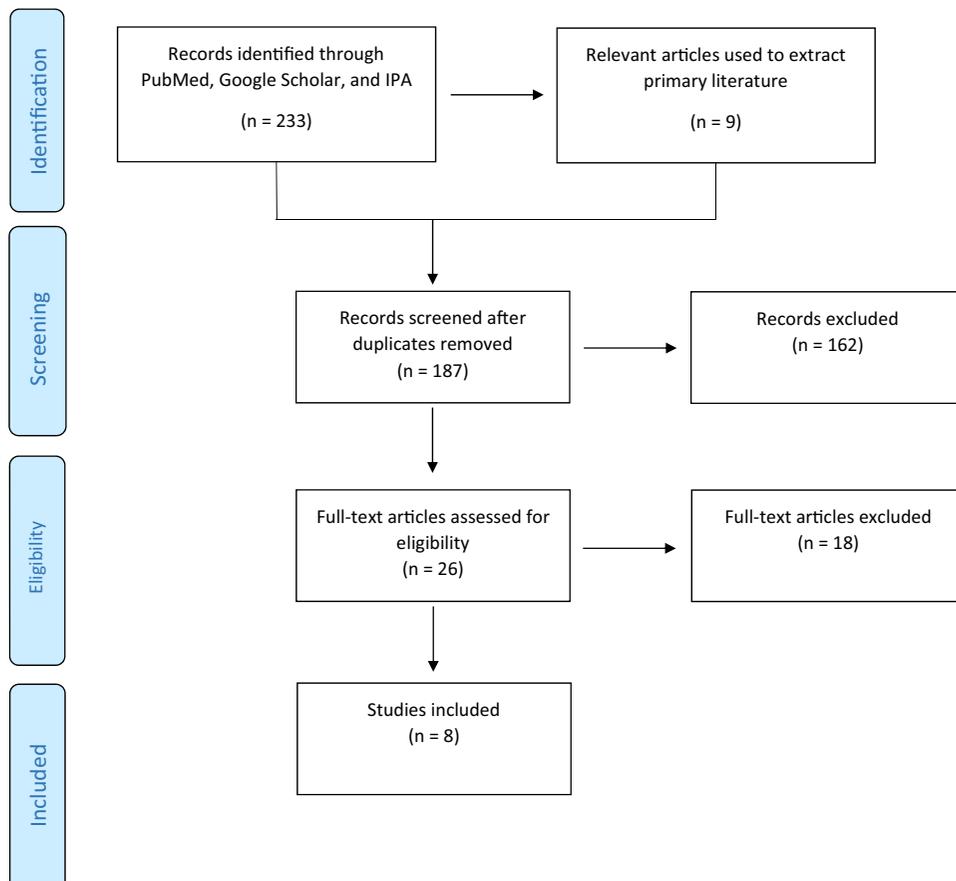


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram. Abbreviation used: IPA, International Pharmaceutical Abstracts.

evaluating CBD in the anxiety response of PTSD, and 5 articles examining CBD in SAD were identified. No articles on the role of CBD in PD, SP, separation anxiety, or OCD management met the criteria for review. Table 1 summarizes the efficacy and safety outcomes of the studies.

Anxiety response in healthy volunteers: Effects of CBD on regional cerebral blood flow

Crippa et al.¹⁷ conducted a double-blind, crossover study in 10 healthy male patients to evaluate the effect of CBD on neural activity of pathways that normally mediate anxiety, measured through neuroimaging. None of the patients nor their first-degree relatives had a history of psychiatric illness. The participants were separated into 2 groups of 5. Regional cerebral blood flow (rCBF) was measured at rest via single-photon emission computed tomography (SPECT), and each participant was evaluated on 2 occasions separated by 1 week.

At the first session, 1 group received 400 mg of CBD while the other group received placebo, both administered as a gelatin capsule in double-blinded fashion. After 90 minutes, SPECT images were taken. In the second session, the procedure was repeated in a crossover design with those who received placebo being administered CBD and vice versa. VAMS was used to assess subjective feelings of anxiety along with physical sedation, mental sedation, and other attitudes and perceptions. VAMS scores were assessed at 30 minutes before CBD or placebo ingestion, at the time of ingestion, and at 60 and 75 minutes following ingestion. A significant reduction in subjective anxiety, measured through VAMS, was noted following CBD administration at all measurements ($P < 0.001$). In the investigators' comparison of rCBF measurements between CBD and placebo ingestion groups, a significantly ($P < 0.001$) increased uptake of the injected ethyl-cysteinate dimer into the medial temporal cortex along with VAMS findings

Table 1
Study summaries: Efficacy and safety of CBD in anxiety disorders

Citation	N	Classification	Study design	Subject(s)	CBD dose and route of administration	Acute versus chronic CBD dosing	Comparison anxiolytic with or without placebo	Measures of anxiety symptoms
Crippa et al., 2004 ¹⁷	10	Anxiety response in healthy volunteers	RCT; crossover	Healthy males without anxiety diagnosis	CBD 400 mg orally x 1 dose, gelatin capsules (n = 10)	Acute	Placebo comparison with crossover (n = 10)	VAMS
Shannon et al., 2019 ¹⁹	72	Anxiety response in patients with either GAD or insomnia diagnosis	Open-label, case series	GAD diagnosis (n = 47; 28 males; 19 females) Insomnia diagnosis (n = 25)	CBD 25–175 mg, dosed daily, oral capsules (n = 72)	Chronic	None	HAM-A
Shannon et al., 2016 ²⁰	1	GAD	Case report	10-year-old female with anxiety diagnosis	Months 1–4: CBD 25 mg dosed daily, capsule Months 4–6: CBD 25 mg dosed daily, capsule; and CBD 6–12 mg as needed for anxiety, sublingual spray	Chronic and acute	None	SCARED
Zuardi et al., 2017 ²¹	59	Healthy volunteer model of SAD	RCT	Healthy males (n = 29) and females (n = 30)	CBD oral capsule x 1 dose: 100 mg (n = 11; 5 males, 6 females) 300 mg (n = 12; 6 males, 6 females) 900 mg (n = 12; 6 males, 6 females)	Acute	Placebo (n = 12; 6 males, 6 females) Clonazepam 1 mg (n = 12; 6 males, 6 females)	VAMS
Zuardi et al., 1993 ²³	40	Healthy volunteer model of SAD	RCT	Healthy males (n = 18) and females (n = 22)	CBD 300 mg, oral gelatin capsule x 1 dose (n = 10)	Acute	Placebo (n = 10) Ipsapirone 5 mg (n = 10) Diazepam 10 mg (n = 10)	VAMS
Linares et al., 2019 ²⁴	57	Healthy volunteer model of SAD	RCT	Healthy males	CBD oral capsule x 1 dose: 150 mg (n = 15) 300 mg (n = 15) 600 mg (n = 12)	Acute	Placebo (n = 15)	VAMS
Bergamaschi et al., 2011 ²⁵	36	SAD diagnosis	RCT	SAD diagnosis (n = 24; 12 males, 12 females) Healthy control patients (n = 12; 6 males, 6 females)	CBD 600 mg x 1 dose, oral gelatin capsules (n = 12)	Acute	Placebo (n = 12; 6 males, 6 females)	VAMS
Crippa et al., 2011 ²⁶	10	SAD diagnosis	RCT; crossover	Males with SAD diagnosis	CBD 400 mg oral x 1 dose, gelatin capsules (n = 10)	Acute	Placebo comparison with crossover (n = 10)	VAMS

Abbreviations used: CBD, cannabidiol; RCT, randomized controlled trial; VAMS, Visual Analogue Mood Scale; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; SCARED, Screen for Anxiety-Related Disorders; SAD, social anxiety disorder.

Table 2
Considerations for CBD

Potential benefit	Potential risks	
Efficacy	Product variability	Drug interactions
Studies have found CBD to be an effective alternative therapy in the acute treatment of anxiety disorders, specifically:	CBD is considered a dietary supplement, and thus lacks standardization in the following areas:	Potential CYP450 interactions: CBD has been found to be a potent inhibitor of CYP3A4 and CYP2D6, increasing the serum level of the following medications:
<ul style="list-style-type: none"> • GAD • SAD • Anxiety related to PTSD 	<ul style="list-style-type: none"> • Dose-effect response • Dosage strength • Route of administration • Purity • Regulation • Product manufacturing • Labeling 	<ul style="list-style-type: none"> • Warfarin • Macrolides • Calcium channel blockers • Antiretrovirals • Antidepressants • Antipsychotics • Opioids
CBD has shown minimal adverse effects compared with existing pharmacotherapy for acute anxiety.	<ul style="list-style-type: none"> • Patient access • Legal status 	It is important to consider patients with potential genetic polymorphisms of CYP450 enzymes: <ul style="list-style-type: none"> • Decreased CYP2C19 or CYP3A4 have potential risk of CBD accumulation.

Abbreviations used: CBD, cannabidiol; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PTSD, posttraumatic stress disorder.

supported the a priori hypothesis that the limbic and paralimbic areas in the brain are likely mediators of CBD's anxiolytic effect. The study results support findings of another study, which found the role of CBD in GAD to occur owing to effects on the limbic and paralimbic regions of the brain.¹⁸ Crippa et al.¹⁷ noted sedation as an observed adverse effect of CBD in the study but did not expound on the magnitude or frequency of this reported effect.

GAD: CBD in anxiety and sleep

Shannon et al.¹⁹ evaluated the use of open-label CBD therapy on anxiety and sleep levels in a case series of 72 adults seen at a psychiatric outpatient clinic over a 3-month timeframe. Patients were included in the study if they had either a diagnosis of anxiety or a sleep disorder and had at least 1 follow-up visit in the clinic after CBD was prescribed. Patients were excluded if they had a sole or primary diagnosis of schizophrenia, PTSD, or agitated depression. Use of other psychoactive medications and adjunctive counseling services did not preclude participation in this study. Patients' anxiety was assessed through the use of validated HAM-A. On HAM-A, anxiety scores range from 0 to 56, with a score below 17 being indicative of mild anxiety and a score above 25 indicating severe anxiety. Safety was assessed through spontaneous self-report in this study. Patients received CBD in fixed doses, ranging from 25 mg/d to 175 mg/d, with the majority of patients receiving the 25-mg daily dose. All patients completed the 1-month follow-up assessment of HAM-A, whereas 56.9% and 37.5% followed up at the 2- and 3-month timeframes for HAM-A, respectively. At the 1-month assessment, the majority of patients (79.2%) experienced an improvement in anxiety based on HAM-A scores. Of those who followed up at the 2-month assessment, 78.1% demonstrated an improvement in anxiety compared with the prior 1-month visit. There was no appreciable difference in mean HAM-A scores between the 2-month and 3-month follow-up assessments (mean HAM-A scores of 16.35 and 16.36, respectively). A few adverse effects were reported in this study: dry eyes, mild sedation, fatigue, and an increase in sexually inappropriate behaviors. The patients who experienced mild sedation reported

resolution within the first weeks of treatment. Furthermore, a small percentage of patients who experienced fatigue or an increase in sexually inappropriate behavior discontinued therapy. The authors concluded that anxiety scores decreased over the course of the study, and the clinical effect on anxiety was maintained throughout the study duration. CBD was well-tolerated and associated with very few instances of treatment discontinuation.

Anxiety response in PTSD: Effectiveness of CBD oil for pediatric anxiety and insomnia as PTSD

A case report by Shannon et al.²⁰ evaluated the effectiveness of CBD oil in anxiety and sleep disorder secondary to PTSD in a 10-year-old girl. The girl had previously been treated with ineffective pharmacotherapy and had experienced adverse effects from the medication. CBD, administered initially as a capsule and subsequently as a sublingual spray for as-needed dosing, was used for the patient's anxiety and insomnia. The patient was also receiving eicosapentaenoic acid fish oil and diphenhydramine with CBD therapy. The patient was originally initiated on a CBD 25-mg capsule dosed daily, which she took for a duration of 4 months as monotherapy. After 4 months, the patient was prescribed adjunct CBD, administered as an as-needed sublingual spray and dosed at 6–12 mg per spray for breakthrough anxiety symptoms. The patient's anxiety was evaluated using SCARED, with a score above 25 indicating a childhood anxiety disorder. A SCARED score was evaluated before initiation of CBD and then monthly for an additional 5 months, for a total of 6 measurements. From baseline to sixth evaluation, the patient's SCARED score decreased from 34 to 18, a 47.06% reduction. No adverse effects of CBD were reported in this case report. The authors concluded that CBD oil may be an effective option to consider when attempting to reduce anxiety secondary to PTSD.

Healthy volunteer models of SAD: Anxiolytic effect of CBD during public speaking in real life

In this double-blinded study, Zuardi et al.²¹ tested the hypothesis that increasing CBD doses would produce anxiolytic

effects in patients with anxiety. Fifty-nine healthy men and women within the age range of 18–35 years were selected for the study. These patients had no diagnosed anxiety disorder, and no disorders involving alcohol or other substance abuse. However, the study was set up to test anxiety levels in public speaking scenarios as a manifestation of SAD. The volunteers were randomly assigned to 5 groups of 12 participants. Each volunteer received either 1 of 3 doses of CBD capsules (100 mg, 300 mg, or 900 mg), clonazepam 1-mg tablet, or placebo in a double-blinded randomized design. VAMS was used in this study to evaluate anxiety levels as well as the sedative effects of CBD. To assess physiological measurements, systolic blood pressure (BP), diastolic BP, and heart rate were recorded. In the procedure, 1 participant was instructed to speak in front of their group. The other participants who were not speaking at the time were instructed to remain silent with a neutral expression. Each member in the group would take their turn to speak. Each participant's VAMS anxiety and sedation score, BP, and heart rate were recorded at baseline, before the speech, during the middle of the speech, and after the speech. Data were compared at the varying time phases. VAMS scores of subjective anxiety were noted to be significantly decreased when the CBD 300-mg group was compared with the placebo and CBD 100-mg groups during the postspeech phase ($P < 0.05$). Similarly, a significantly greater decrease in VAMS was noted in the comparison of the CBD 300-mg group with the CBD 900-mg group in the speech phase ($P < 0.05$). Higher sedative effects were noted with clonazepam in comparison with the CBD and placebo groups among the phases ($P < 0.05$). The authors concluded that the CBD 300-mg dose had a greater therapeutic effect on anxiety when compared with the 100-mg and 900-mg doses. These results confirmed prior study findings and suggested that CBD induces acute anxiolytic effects with an inverted U-shaped dose-response curve in humans—an effect that, at this time, is not fully understood and should not be considered as an absolute pharmacodynamics principle.^{21,22}

Effects of ipsapirone and CBD on human experimental anxiety

In a double-blinded study, Zuardi et al.²³ used 40 healthy subjects separated into 4 groups of 10 who received either oral CBD 300 mg, diazepam 10 mg, ipsapirone 5 mg, or placebo. The volunteers were subjected to a simulated public speaking test (SPST) to compare the anxiolytic properties of the assigned drug. The effects of these drugs were measured using VAMS, STAI, and BSS, which evaluates somatic symptoms (fatigue, weakness) that would indirectly affect anxiety. After a 15-minute adaptation period, baseline measures were collected before the intervention (drug or placebo) was given. One hour and 20 minutes after the drug was taken, prestress measures were collected. After collection, the subjects watched a video with instructions about the task they would be performing. Each subject had 2 minutes to prepare a 4-minute speech about a topic covered previously in a university course and was told the speech would be recorded and analyzed by a psychologist. Anticipatory anxiety measurements were taken before the subject began speaking. During the middle of the speech, researchers interrupted the subject and subjective anxiety measurements were collected. Fifteen minutes after the speech ended, poststress measurements were collected. The VAMS results of the study demonstrated

that there was a significant increase in subjective anxiety in all groups ($P < 0.001$) during the SPST procedure. Diazepam significantly decreased subjective anxiety throughout the study when compared with placebo ($P = 0.016$). Specifically, diazepam decreased prestress ($P = 0.042$) and poststress ($P = 0.002$) measurements. However, diazepam also significantly increased feelings of physical sedation at the prestress ($P = 0.036$) and anticipatory anxiety ($P = 0.003$) measurements. Ipsapirone significantly decreased performance anxiety ($P = 0.037$) measurements when compared with placebo, while CBD significantly decreased poststress anxiety ($P = 0.017$) measurements. Only diazepam showed significant physical and mental sedative effects, which may limit its therapeutic application in some patients. The authors concluded that acute administration of CBD or ipsapirone may have beneficial alternative anxiolytic effects when used in healthy subjects and may be appropriate alternatives for those experiencing sedative effects from other anxiolytic medications.

CBD presents an inverted U-shaped dose-response curve in a SPST

Linares et al.²⁴ conducted a double-blind, placebo-controlled trial of 57 healthy adult males who were randomized to receive either placebo or CBD dosed at 150 mg, 300 mg, or 600 mg daily before SPST. The SPST was administered according to the Bergamaschi procedures.²⁵ VAMS was used to assess subjective anxiety. In the analysis of variance test of group comparisons, there were no significant findings among groups and phases of the SPST ($P = 0.1$). A post hoc analysis among groups during the phases of SPST indicated that patients in the CBD 300-mg group demonstrated lower anxiety levels in the speech phase than the placebo group ($P = 0.042$). The study investigators inferred an inverted U-shaped dose-response curve based on VAMS results with sequential CBD doses, with the 150-mg and 600-mg doses associated with minimal anxiolytic effects and the intermediate 300-mg dose producing the most clinically significant outcome on anxiety. This result supports findings from previous studies.^{21–23} No safety outcomes were reported in this study.

SAD: CBD reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients

In a double-blind, randomized, controlled clinical trial, Bergamaschi et al.²⁵ compared the effects of taking oral CBD 600 mg with those of taking placebo in SPST. A total of 36 patients were included in the study; 24 were treatment-naïve patients with SAD and 12 served as healthy controls (HCs) who did not receive medications. Of the 24 treatment-naïve patients with SAD, 2 separate groups of 12 were formed randomly. One group received CBD while the other received placebo, both packed in identical gelatin capsules. Subjective ratings using VAMS, SSPS-N, and physiological measures such as BP, heart rate, and skin conductance were all measured at 6 different time points during SPST. The time points of evaluation were selected for full evaluation of anxiolytic effects seen with CBD compared with those seen with placebo. In the first stage of the procedure, a single dose of CBD or placebo was administered in a double-blind fashion along with administration of baseline measurements. In the second phase, participants were given instructions to prepare a 2- to 4-minute speech that would be videotaped and analyzed by a

psychologist. Researchers collected anticipatory speech measurements before the public speaking occurred. Interruptions in the speech were made in the middle and speech measurements were again taken. The speech was allowed to continue for another 2 minutes and then concluded, and 2 postspeech measurements were made 15 minutes and 35 minutes after the speech. After analyzing the results from the study, the VAMS scale showed that the placebo group presented with significantly higher anxiety levels with greater cognitive impairment, discomfort, and alertness as compared with the HCs. The pretreated CBD SAD group had significantly reduced anxiety, cognitive impairment, and discomfort during the speech performance compared with the placebo group ($P = 0.009$). An important observation made by the authors was that negative self-evaluation was almost abolished by CBD. There were no significant differences found in vital signs. Overall, the effects of single dose CBD in patients experiencing SAD show a promising impact with a rapid-onset therapeutic effect.

Neural basis of anxiolytic effects of CBD in generalized SAD

In a double-blinded preliminary report, whose purpose was to confirm the hypothesis that CBD may be effective in treating SAD, Crippa et al.²⁶ assessed 10 men with generalized SAD, which was confirmed by the structured clinical interview (SCID) for *DSM-IV*. All the subjects in the study were determined to have a severe social phobia. To analyze the effects of CBD in these patients, researchers evaluated each subject using the VAMS assessment. During the test, subjective ratings on VAMS were made 30 minutes before the ingestion of the drug (prestress), at the time of drug ingestion (adaptation), and at 75 minutes after ingestion (poststress). Functional neuroimaging was used to determine the neurophysiologic effect of CBD in patients with SAD. SPECT imaging was used to compare the effects of CBD and placebo on rCBF. This process was completed in a double-blind, randomized, repeated measures, within-subject crossover design using a dose of 400 mg of CBD given in oral gelatin capsules. In the first session, the men were given CBD 400 mg or placebo. In the second session, this exercise was performed again, but this time the men who had received CBD earlier were administered the placebo and vice versa.

Upon analysis of the VAMS score, the study showed that acute administration of CBD reduced subjective anxiety in patients clinically diagnosed with an anxiety disorder, in this case SAD. Specifically, CBD showed a significantly faster time onset of decreasing anxiety ($P < 0.001$) in the patient compared with placebo. Based on the VAMS score numbers, those taking CBD began with a mean assessment at prestress anxiety of 48.3 and ended poststress anxiety with 30.8, a decrease of 36.23%. Patients in the placebo group began prestress at an anxiety level of 46.9 and ended with a poststress anxiety level of 42.1, a decrease of only 10.23%. The SPECT imaging was able to show that CBD was active in the paralimbic and limbic areas. Overall, the authors concluded that CBD has important advantages in treatment of SAD, such as a minimal adverse-effect profile and early onset of action. However, the authors also concluded that more double-blind, placebo-controlled studies are needed to evaluate the long-term effects of CBD for treatment of anxiety disorders. Last, investigators suggested the need for further research and

definitive conclusions on whether a relationship exists between rCBF and CBD plasma levels, which would potentially provide a less invasive strategy for monitoring CBD's clinical effects.

Discussion

CBD has been studied for use in treating anxiety-like responses for more than a decade.²⁷ Several early studies evaluated the use of CBD in preventing neural responses to fearful faces.^{28,29} Initial studies evaluating the difference in response between CBD and THC showed that while THC use often results in negative behavioral and psychological effects, CBD is safe and well-tolerated with no difference from placebo in regard to increasing unwanted anxiety, sedation, positive psychotic symptoms, and intoxication.^{28,30,31} In addition, CBD may even have utility in minimizing the negative effects of THC.³²

On the basis of the results of currently available published human studies, it is seen that CBD has demonstrated a developing role as an alternative therapy in the indications of anxiety disorders, specifically GAD, SAD, and anxiety related to PTSD. Because the majority of the reviewed studies had small sample sizes, low statistical power posed a notable limitation. Primarily adult, male patients were enrolled in the studies, with only 1 pediatric case report meeting criteria for review. In addition, several studies enrolled healthy volunteers modeling varying anxiety disorders. Very few studies that enrolled patients with an anxiety diagnosis and compared the outcomes of taking CBD with those of taking placebo were identified. Taken together, these overall study characteristics may limit the generalizability of results. Similarly, because wide ranges of CBD doses were implemented among the studies, future evaluations of more intermediate range CBD doses may be warranted to determine optimal dosing definitively. Last, many studies made conclusions related to the dose-response curve of CBD on the basis of the results of neuroimaging findings and subjective scores on anxiety assessments without assessing plasma levels; therefore, these findings should be interpreted with caution.

In the studies reviewed, CBD regularly showed improved clinical outcomes in GAD, SAD, and anxiety related to PTSD, with minimal adverse effects, which differs from other therapeutic agents that are currently used for these indications. These results indicate that CBD could provide a unique therapeutic opportunity to augment or replace existing pharmacotherapy in patients with inadequate relief while causing fewer adverse effects. While CBD did show positive benefits in these patient populations, it can be challenging to translate results across studies owing to the lack of a standardized assessment tool and the variety of dosing schedules and routes of administration that were used. The most regularly used screening tool in CBD studies is VAMS, but its use has not been universal. Further standardized approaches in dosing and outcome measurement will be useful to best determine an effective therapeutic dose of CBD for broader patient populations.

Of note, the increasing amount of human studies evaluating the role of CBD in the treatment of anxiety and anxiety-related disorders are showing potential therapeutic success, specifically when CBD is administered with acute dosing. Fewer studies exist that evaluate the safety and efficacy of long-term

use of CBD in human populations. While clinical evidence supporting the use of CBD in these patient populations now exists, there continue to be considerable challenges in terms of a lack of standardized dosage and route of administration. These challenges also persist in terms of lack of standardization in product manufacturing. Typically, CBD products are labeled not by strength per dose, but by strength of product contained in the entire package. The labeling of these products can lead to confusion for patients attempting to follow a specific dosage schedule based on their clinical indication, suggesting a need for focused patient education and follow-up with patients initiating CBD therapy for a chronic indication.

While CBD has a generally mild adverse-effect profile as demonstrated through human studies, some clinical considerations do exist. Clinical data have demonstrated the potential for CBD to increase plasma levels of warfarin, and suggest that CBD products may potentiate some drug interactions via CYP450 pathways.³³ CBD has the potential to function as a potent inhibitor of CYP3A4 and CYP2D6, which may result in increased serum concentrations of medications such as macrolides, calcium channel blockers, antiretrovirals, antidepressants, antipsychotics, and opioids.^{34,35} In addition, patients with decreased CYP2C19 or CYP3A4 function may be at risk for increased CBD accumulation and exposure, while patients taking a CYP3A4 inducer may see a decrease in CBD exposure.^{33,35} Patients taking anticoagulants or other interacting medications should be counseled about the effects of initiating and discontinuing CBD products. See Table 2 for a list of other CBD considerations.

Another potential challenge surrounding the use of CBD in the general population concerns the persistent issues regarding product purity. Generally, CBD products sold to the public for medical use contain high levels of CBD and low levels of THC, although these levels of THC may range between 0.3% and 5% based on state law.³⁶ Even with the level of THC provided on product labeling, actual content of THC may be higher than what is listed on the label as found in FDA test results of products in 2015 and 2016.^{37,38} For patients where the presence of THC could be problematic because of workplace drug screenings or because the legal status of cannabis products in their state is in question, these factors should be considered before recommendation of CBD products. In addition, because of the lack of product regulation for safety and purity given its status as a dietary supplement, products may also have a variable level of CBD present in them, further increasing difficulty in ensuring that patients receive a desired dose to obtain a specific therapeutic effect. One study in 2015 demonstrated a wide range of product content of CBD, with products sold as medical cannabis products being both over- and underlabeled in regard to CBD content.³⁹ Both regulation and increased quality assurance are needed for CBD products to be routinely recommended for use as a medical product.

Last, patient access to CBD products can vary. While all 50 states have legislation that legalizes CBD products, restrictions vary widely, and CBD products are still considered by the federal government to be in the same restricted access class as marijuana. In similar fashion to their approach to medical marijuana, the federal government generally declines to enforce restrictions on CBD use. The legal status of CBD is evolving, and clinicians should pay careful attention to the laws surrounding CBD sales and usage in their states.

Conclusion

CBD has consistently demonstrated acute reduction in anxiety-related symptoms in patients, specifically within GAD and SAD. Additionally, the use of CBD for these disorders has shown increasingly minimal adverse effects compared with existing pharmacotherapy. Further studies are needed to determine long-term safety and efficacy of CBD products and a more standardized dose-effect response. Clinicians should be mindful of challenges related to product purity, legal status of CBD based on geographic area, and the potential for drug interactions when recommending the use of CBD for anxiety.

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Cannabidiol's role in anxiety management

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- Jessica W. Skelley, PharmD, BCACP**, Associate Professor of Pharmacy Practice, McWhorter School of Pharmacy, Samford University, Birmingham, AL
- Crystal M. Deas, PharmD, BCPS**, Assistant Professor of Pharmacy Practice, McWhorter School of Pharmacy, Samford University, Birmingham, AL
- Zachary Curren, BS**, Student Pharmacist, McWhorter School of Pharmacy, Samford University, Birmingham, AL
- Jonathan Ennis, BS**, Student Pharmacist, McWhorter School of Pharmacy, Samford University, Birmingham, AL



Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users



Jasmine Turna^{a,b}, William Simpson^b, Beth Patterson^{b,c}, Philippe Lucas^{d,e},
Michael Van Ameringen^{b,c,f,*}

^a Neuroscience Graduate Program, McMaster University, 1280 Main St W, Hamilton, ON, L8S 4L8, Canada

^b MacAnxiety Research Centre, McMaster University, L02-1057 Main St W, Hamilton, ON, L8S 1B7, Canada

^c Department of Psychiatry and Behavioural Neurosciences, McMaster University, 1280 Main St W, Hamilton, ON, L8S 4L8, Canada

^d Social Dimensions of Health Graduate Program, University of Victoria, 3800 Finnerty Rd, Victoria, BC, V8P 5C2, Canada

^e VP, Patient Research & Access, Tilray, 1100 Maughan Rd, Nanaimo, BC, V9X 1J2, Canada

^f Michael G. DeGroot Centre for Medicinal Cannabis Research, McMaster University, 1280 Main St W, Hamilton, ON, L8S 4L8, Canada

ARTICLE INFO

Keywords:

Cannabis
Anxiety
Depression
Survey
Medicinal

ABSTRACT

Cannabis is commonly used recreationally for its euphoric and relaxing effects, while its medical use is permitted in several jurisdictions. With only low-quality evidence suggesting anxiolytic effects of cannabis and strong public sentiment surrounding such purported effects, the purpose of this study was to examine the prevalence of cannabis for medicinal purposes (CMP) use for anxiety symptoms. An online survey was disseminated to CMP users registered with a Canadian licensed producer. Respondents completed demographic and validated self-report questionnaires (GAD-7, PHQ-9, MINI-SPIN, and panic disorder/agoraphobia DSM-5 criteria). Cannabis use behaviors were also discussed. Overall, 2032 completed responses with a verified user number were collected. Of the total sample, 888 (43.7%) reported CMP authorization to treat anxiety symptoms and completed all psychometric screening instruments. Rates of probable disorders were high (Generalized Anxiety Disorder: 45.6%, Social Anxiety Disorder: 42.4%, Major Depressive Disorder: 25.7%, Panic Disorder/Agoraphobia: 25.7%); 63.4% met screening criteria for ≥ 1 disorder. Most (92%) reported that cannabis improved their symptoms, despite continuing to endorse moderate-level severity. Nearly half (49%) reported replacing a non-psychiatric (53.7%) or psychiatric medication (46.3%) prescribed to them by their physician with CMP. Respondents endorsed daily CMP use and severity of anxiety (GAD-7, $p < 0.001$) and depressive (PHQ-9, $p < 0.001$) symptoms were positively associated with the amount of cannabis used/day. The vast majority perceived symptom improvement with CMP use and did not believe CMP use was associated with impairment or an inability to control use. Nevertheless, the possibility of cannabis use disorder cannot be ruled out as well as the possibility that improvements in non-psychiatric conditions were attributed to improvements in anxiety. These results highlight the need to systematically evaluate CMP use for mental illness.

1. Introduction

Cannabis is commonly used recreationally for its euphoric and relaxing effects. The dried plant is typically smoked or vaporized and also consumed in foods or used as a concentrated oil. Although considered an illicit substance in many parts of the world, regulatory bodies in the Netherlands, and several US states have legalized medicinal and/or recreational use, with Canada having legalized recreational use on October 17, 2018. Prior to this, only cannabis for medicinal purposes (CMP) could be legally obtained from licensed producers for a myriad of medical conditions, with appropriate physician authorization. A

recent meta-analysis revealed moderate-quality evidence to support cannabinoid treatment of chronic pain and spasticity, with very low-quality evidence suggesting improvement in anxiety and no effect in depression (Whiting et al., 2015). Only small studies of synthetic cannabinoids (Fabre and McLendon, 1981; Glass et al., 1981; Ilaria et al., 1981; Lee, 2009) or cannabidiol (CBD) (Bergamaschi et al., 2011; Crippa et al., 2011) have been examined in clinically anxious populations. Yet, many Canadians report using cannabis to alleviate self-reported anxiety (Walsh et al., 2013).

Anxiety disorders are chronic conditions with a lifetime prevalence of 31.6% (Kessler et al., 2012). They include social anxiety disorder

* Corresponding author. Present/Permanent Address: MacAnxiety Research Centre, L02-1057 Main Street West, Hamilton, Ontario, L8S1B7, Canada.
E-mail address: vanamer@mcmaster.ca (M. Van Ameringen).

(SAD), generalized anxiety disorder (GAD), panic disorder (PD) and specific phobias. These disorders are associated with significant burden for afflicted individuals, their families and society (Katzman et al., 2014). While many established efficacious first-line treatments exist, including antidepressants and cognitive-behavioral therapy, 40–60% of patients continue to have residual, impairing symptoms while others are non-compliant or have difficulty accessing treatments (Katzman et al., 2014). Given such limitations, individuals may seek alternative treatments and public sentiment surrounding cannabis' purported anxiolytic effects suggest cannabis may fulfil this role.

The primary active components in cannabis are Δ^9 -tetrahydrocannabinol (THC) and CBD. While THC is thought to have anxiolytic, antidepressant and hypnotic effects, CBD has demonstrated anti-inflammatory, analgesic, anticonvulsant, and anxiolytic properties, (Walsh et al., 2017). Of the two primary cannabinoids, THC is the psychoactive constituent and at higher doses has been documented to induce panic, paranoia and anxiety, (D'Souza et al., 2004; Fusar-Poli et al., 2009). The ratio of these cannabinoids varies greatly between strains of cannabis and consequently may induce a wide variety of effects. For instance, when CBD is administered with THC, it has demonstrated an ability to “undo” the unwanted and anxiogenic effects of THC by acting as a pharmacological antagonist (Karniol et al., 1974; Zuardi et al., 1982). Given the various cannabinoids and other active compounds in the cannabis plant, it is difficult to discern the specific behavioral effects of cannabis. As such, the existing cannabis literature comprised of studies of pure or synthetic cannabinoids may not be a sufficient proxy to illustrate cannabis' potential anxiolytic effects. Canadians are currently using cannabis for anxiety symptoms (Sexton et al., 2016; Walsh et al., 2013) but whether these individuals are treating state anxiety or symptoms of a clinical disorder remains unclear. With the scientific literature indicating cannabis as a non-evidence-based treatment for anxiety, mood and related disorders (Turna et al., 2017), this study examines the prevalence of CMP use for anxiety, psychiatric symptom severity and CMP use behaviors in a sample of authorized Canadian medicinal cannabis users.

2. Methods

2.1. Study population and design

An online survey was disseminated to all authorized CMP users registered with Tilray (British Columbia, Canada, $n = 16,675$) on January 9, 2017, and was closed 48 h later. Respondents received a \$10 account credit towards future Tilray purchases. Following acknowledgement of a disclosure statement, information regarding demographics and CMP use was collected. Questions were structured in multiple choice, checklist and rating scale format. Individuals were not able to skip question(s) they did not wish to answer, therefore, all completed questionnaires did not contain missing data. Many questions contained “skip logic”, so that if the respondent answered “no”, they did not complete further questions concerning this topic. Study data was collected and managed using Research Electronic Data Capture (REDCap) (Harris et al., 2009), a Health Insurance Portability and Accountability (HIPAA) and Personal Information Protection and Electronic Documents Act (PIPEDA) compliant online survey tool allowing participants to directly enter responses.

2.2. Outcome measures

All respondents answered questions regarding primary illness and symptoms treated with CMP. Those who identified anxiety as one of their primary symptoms treated with CMP in the second question then completed validated self-report symptom severity scales to characterize psychiatric morbidity including: 1) the GAD-7: a 7-item questionnaire used to screen for GAD and anxiety symptom severity, a score ≥ 10 was used to suggest moderate anxiety (Spitzer et al., 2006); 2) The Patient

Health Questionnaire (PHQ-9) is a multipurpose instrument for screening, monitoring and measuring depressive symptom severity with a total score ≥ 15 suggesting moderately severe depression (Kroenke et al., 2001); 3) The MINI Social Phobia Inventory (Mini-SPIN) is a validated 3-item scale in which a total score ≥ 6 indicates significant SAD symptoms (Connor et al., 2001). Given that no brief measure for panic disorder was found in the literature, four screening questions from the Panic Agoraphobia Scale (PAS) (Bandelow, 1995) were included, and a positive screen for potential panic disorder symptoms was coded if respondents identified the presence of panic attacks and reported > 1 panic attack in the past 2 weeks. Respondents were instructed to answer questions based on the past two weeks. Additional questions regarding CMP use and its effect on symptoms were also incorporated. The survey included 25 anxiety-related questions.

2.3. Statistical analysis

Descriptive statistics, including means, standard deviations and percentages were used to describe demographics, perceived efficacy, conditions, etc. Data analysis was performed using R (version 3.3.1, R Core Team). Frequencies were compared using a chi-square test. A one-way ANOVA or *t*-test was used to examine mean differences between groups, where applicable.

2.4. Ethics approval

This study was approved by the Institutional Review Board Services.

3. Results

In total, 3405 responses were received and 2032 responses were paired with a verified user number. Of the total sample, 888 (43.7%, ANX group) identified anxiety as one of the primary symptoms for CMP use from a list of 14 prepopulated medical symptoms. These respondents were asked to complete all symptom severity screening questionnaires.

3.1. Sample demographics

The mean age of the ANX group was 36.3 ± 10.8 years (range: 16–84 years). The sample was primarily male (58.2%), married (36.1%), employed full-time (50.3%), living in an urban area (43.6%) and with a college education (32.2%); additional demographic characteristics can be found in Table 1. This sample was prescribed CMP by 607 different physicians.

3.2. Psychiatric comorbidity

Based on the cut-off for each respective screening tool, rates of probable anxiety and depressive disorders within the ANX were high (Table 2). In this sample 63.4% met screening criteria for ≥ 1 disorder.

The severity of anxiety (GAD-7) and depressive (PHQ-9) scores were positively associated with the amount of cannabis used per day. This was examined using a one-way ANOVA with GAD-7 score as the dependent variable and low (< 1 g/day), moderate (1–2g/day) or high (≥ 3 g/day) CMP use as the independent variables. Post-hoc comparisons revealed that high users had significantly higher GAD-7 (11.5 ± 5.8) and PHQ-9 (11.8 ± 6.9) scores than moderate (GAD-7: 9.1 ± 5.3 ; PHQ-9: 9.5 ± 6.6) or low users (GAD-7: 9.3 ± 5.3 ; PHQ-9: 9.8 ± 6.1) (GAD-7: $F(2,771) = 14.0$, $p < 0.001$; PHQ-9: $F(2,771) = 9.3$, $p < 0.001$). No differences were observed between low and moderate users.

3.3. Psychiatric effects of CMP use

To better understand perceived efficacy of CMP for symptomatic

Table 1
Demographic characteristics of ANX sample.

Characteristic (n = 888)		%	Characteristic (n = 888)		%
Sex	Male	58.2	Employment	Full-time	50.3
	Female	41.5		Part-time	13.0
	Other	0.3		Unemployed (looking for work)	11.1
Marital Status	Married/Common-law	61.1		Unemployed (not looking for work)	5.4
	Single	31.1		Retired	2.5
	Divorced/Separated	7.1		Disabled	17.7
	Widowed	0.7			
Education	High School or less	25.0		Annual Household Income	≤ \$39,000
	Some college/university	23.5	\$40,000 - \$69,999		26.8
	Technical/non-university degree	32.2	\$70,000 - \$99,999		16.3
	University degree	14.8	≥ \$100,000		16.4
	Graduate degree	4.5	Ethnicity	Caucasian	85.1
Province	Alberta	64.2		More than one race	5.4
	Ontario	19.7		Metis	1.9
	British Columbia	6.0		Asian	1.7
	Other Provinces	10.1		Other ^a	5.9

^a Other: Aboriginal, South Asian, Black, Hispanic and 'Other'.

Table 2
Prevalence of anxiety and depressive disorders in ANX as per self-report screening measures (n = 888).

Disorder	Diagnostic cut-off score	Prevalence (%)	Mean Score
GAD	GAD-7 ≥ 10	45.6%	9.8 ± 5.5
SAD	Mini-SPIN ≥ 6	42.4%	4.9 ± 3.5
MDD	PHQ-9 ≥ 15	25.7%	10.4 ± 6.4
PD/agoraphobia	Modified PAS criteria	25.7%	NA

relief, the ANX group was asked to identify the anxiety and depressive symptoms CMP use improved, using 21 prepopulated choices (allowed to check all that applied). The majority of the ANX group reported that CMP improved their “anxiety, worry, fears” (92.0%), “irritability” (75.5%), “difficulty falling to sleep” (72.4%), “anxiety attacks” (58.8%) and “low mood” (56.9%) (Fig. 1). When asked how effective CMP was at relieving these symptoms on a scale of 1 (not at all effective) to 5 (very effective), 64.9% reported a rating of 4 or more; only 1%

responded “not at all effective”. Respondents using > 3 g cannabis/day reported significantly greater perceived benefit related to cannabis use as compared to individuals using < 3 g/day (p < 0.0001).

Many in the ANX group reported using cannabis to feel relaxed (84.4%). Respondents were also asked which cannabis strains were thought to best improve their anxiety and which strains they found to worsen their anxiety. They could select as many of the 6 prepopulated options available. *Cannabis indica* was more often reported to have a subjective anxiolytic effect (51.5%), while *Cannabis sativa* was the most frequently reported anxiogenic strain (32.3%) (Fig. 2).

3.4. Cannabis use behaviors

A majority of the ANX group used cannabis recreationally (99.5%) prior to medicinal use. However, 85.5% reported trying at least 1 traditional mental health treatment before CMP ($\bar{x} = 2.6 \pm 2.0$ treatments), with 55.5% reporting medication and 20.5% reported cognitive-behavioral therapy. Use of other cannabinoid drugs was relatively

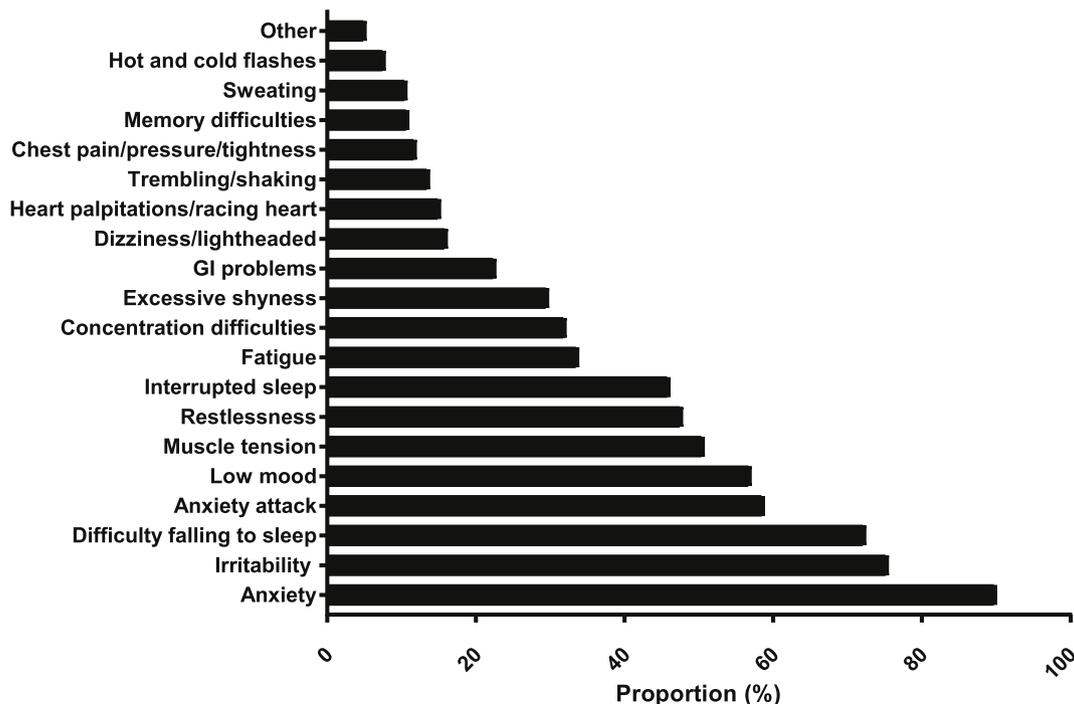


Fig. 1. Symptoms of anxiety and depressive disorders reported to be relieved by CMP use in ANX group (n = 888).

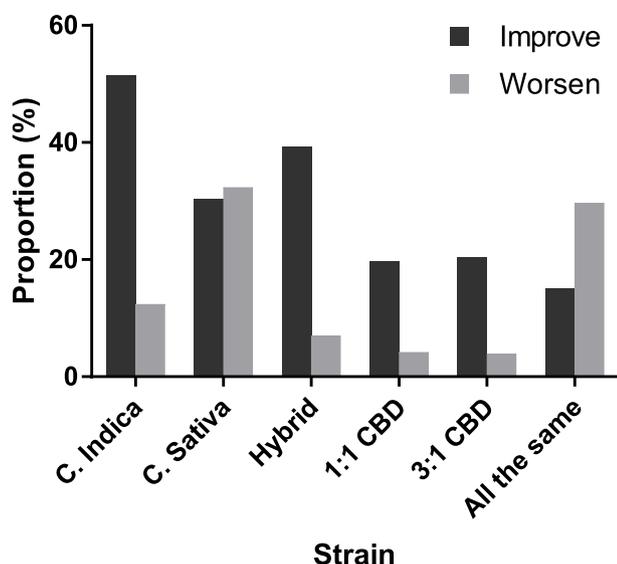


Fig. 2. Subjective reports of anxiogenic versus anxiolytic effects of varying cannabis strains (n = 888).

low (Dronabinol:1.0%, Nabilone:5.9%, Sativex:1.6%, Other Cannabinoids:0.6%). Fifty respondents (6%) endorsed having a primary mental health condition and had no previous treatment prior to their CMP. Although not significant, these individuals tended to be male, have lower levels of education and endorsed that cannabis is safer than prescription medication compared with respondents who had tried at least one traditional treatment. They also reported significantly younger mean age of recreational cannabis use (15.96 vs. 17.48, $t(99.97) = -2.5571, p = 0.01$).

In total, 22.1% of respondents stated that their use of cannabis had increased “a lot” since obtaining access to CMP, with 42% of individuals using 1–2 g of cannabis per day. Thirty-five percent reported using < 1 g/day while 23% of the sample used ≥ 3 g/day. Respondents did not believe they had difficulty controlling CMP use (79.7%) or that their social and leisure activities were impaired by it (84.4%). Most respondents also reported vaporizing (47.6%) as the preferred mode of delivery, followed by oral ingestion (21.4%, includes edibles, oils, etc.), joints (18.5%), etc.

Respondents were also asked which prescription drugs they had replaced with cannabis (up to 3 answers permitted) and at what rate they were substituting the prescription medication with CMP. Nearly half of the ANX sample (49%) reported substituting a prescribed medication with CMP to some degree, of whom 61% indicated that cannabis had completely (100%) replaced a drug prescribed to them by their physician for a given medical condition (Table 3). We also compared the rates of substitution between individuals with and without

Table 3

Proportion of the ANX sample replacing a prescribed medication with medicinal cannabis (n = 888).

Drug Class	%
Antidepressants	23.8
Opioid	19.2
Benzodiazepine	15.8
NSAIDs	6.1
Antiepileptic	5.0
Sedative-Hypnotic	4.2
General Analgesic	3.9
Psychostimulant	3.7
Antipsychotic	3.0
All others	15.3

Table 4

Frequencies of primary condition for which CMP has been authorized by a medical doctor.

Indication	ANX group (n = 888)	All respondents (n = 2032)
Mental Health (Stress, Anxiety, Depression, PTSD, eating disorders)	52.9%	30.6%
Chronic Pain	17.2%	26.7%
Insomnia	8.0%	9.4%
Other	5.0%	8.9%
Arthritis	3.5%	7.7%
All others	13.4%	16.7%

anxiety. No significant differences in medication substitutions or CMP usage patterns were found between those with anxiety and those without.

3.5. Primary condition for CMP

Among all respondents (n = 2032), mental health (30.6%) was most frequently identified as the primary medical condition currently being treated with CMP. Mental health (52.9%) was also the most frequent indication in the ANX group (n = 888) (Table 4). Demographic characteristics and cannabis use behaviours were compared among individuals in the ANX group who were prescribed CMP to treat a mental health condition (52.9%) versus those taking CMP for a non-psychiatric condition (47.1%). Respondents who were prescribed CMP for a non-psychiatric condition appeared to use slightly more cannabis ($\chi^2(6) = 19.339, p = 0.004$) and were more likely to be on disability ($\chi^2(5) = 33.15, p < 0.001$; 24.1% vs. 11.9%) than respondents prescribed CMP to treat a mental health condition. Although not significant, most respondents using CMP for a non-psychiatric condition were male, married, living in a suburban area and have a technical or non-university degree. No significant differences were found between groups in terms of level of income, province of residence, scores on the PHQ-9 or GAD-7 nor in the perceived benefit of cannabis use.

4. Discussion

The primary finding of this study is the high frequency of CMP use for the treatment of self-reported anxiety symptoms (43.7%, ANX). Almost 2/3 of the ANX group met screening criteria for ≥ 1 disorder (63.4%), with GAD and SAD being the most common (Table 2). Similarly, anxiety and depressive scores were also higher in those using more cannabis (using ≥ 3 g/day). Although the majority of participants reported that CMP use improved their anxiety symptoms (Fig. 1), severity measures indicated at least ongoing moderate symptoms (Table 2). This suggests that even if cannabis has been helpful for these individuals, it may not be effectively decreasing symptoms to a clinically significant level. For instance, their symptoms may have previously been more severe and have, with CMP use, decreased to a moderate level. An alternative explanation may be that the improvement noted by CMP users in anxiety may be related to the relief of cannabis-withdrawal associated anxiety symptoms. Or that this improvement may have been confounded by improvements in the non-psychiatric conditions also treated with CMP. Mental health conditions were the leading indication for CMP authorization in both the ANX group and the overall sample (Table 4). Many were also replacing prescribed medications with CMP. The most frequently replaced drugs included psychotropics (antidepressants and benzodiazepines) and pain relievers (Table 3). While most denied social impairment and difficulty controlling use, many would be considered heavy users due to daily use. Cannabis indica, followed by hybrids, were most often rated as anxiolytic (Fig. 2). Interestingly, both strains contain high THC (above

18%) and relatively low CBD (1%). Although THC has been purported to have anxiolytic properties, it has also been associated with the development of panic, paranoia and anxiety, D'Souza et al., 2004; Fusar-Poli et al. (2009). Furthermore, while pre-clinical research suggests that CBD may be anxiolytic (Bergamaschi et al., 2011; Crippa et al., 2011), it is critical to note that the vast biochemical variability of these plants makes it difficult to discern which effects are attributable to which compound. Rather, the notion of an “entourage effect” or synergistic effect between the many cannabinoids, terpenoids and flavonoids (Elzinga et al., 2015) may provide one possible explanation of the reported anxiolytic properties of *Cannabis indica* and hybrids in this sample.

The prevalence of CMP use for anxiety in our sample exceeded what has been previously reported. An older study reported less than 10% of authorized Health Canada CMP users were prescribed cannabis for anxiety, while non-authorized use was significantly higher (Walsh et al., 2013). Canadian regulations surrounding CMP authorization have become more inclusive since this study in 2013, now requiring physician authorization for any condition the physician feels warrants cannabis treatment. This process involves acquiring a medical document which includes the name of the healthcare practitioner and patient, daily CMP quantity prescribed and duration of use; this document is then submitted to the licensed producer (Health Canada, 2017). This change is likely reflected in the considerable increase of authorized users in our sample using cannabis for anxiety. Despite these changes in CMP legislation, the scientific evidence examining cannabis treatment in anxiety disordered clinical populations is still in its infancy. When using the four levels of evidence as defined by the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Kennedy et al., 2016), the existing cannabis literature would be considered Level Three evidence for certain mental health conditions including social anxiety disorder, posttraumatic stress disorder and Tourette's Syndrome (Turna et al., 2017). The increasing number of CMP authorization for mental health issues, reveal that Canadian physicians are being approached for CMP prescriptions to treat these conditions and/or may be willing to prescribe for these symptoms despite a dearth of supporting evidence examining the efficacy and safety of CMP in anxiety.

There is strong public sentiment regarding CMP efficacy for a wide range of medical conditions, including subjective anxiolytic effects (Sexton et al., 2016). However, this is the first study to characterize symptom severity beyond subjective reports of anxiety noted in previous studies (Sexton et al., 2016; Walsh et al., 2013). Validated clinical self-report measures revealed clinically significant psychiatric symptoms in our sample, with 63.4% meeting criteria for at least 1 disorder. Yet, respondents perceived CMP treatment as efficacious for their anxiety symptoms. Given that the symptom severity measures used in this survey have demonstrated sensitivity to change with treatment in clinical trials, these results elude to a possible disconnect between respondent belief regarding CMP efficacy and quantifiable symptom improvement. Furthermore, respondents using > 3g/day also reported greater perceived benefit, yet endorsed higher anxiety and depression symptoms. This finding can be interpreted in several ways: these individuals may be using more cannabis because they are more symptomatic; perhaps cannabis used in this group is not reducing anxiety/depressive symptoms but is providing an improved sense of well-being; or perhaps this a group of patients who have problematic use, as there is some evidence to suggest that higher daily use of cannabis is associated with cannabis use disorder (CUD) (van der Pol et al., 2015). However, we have no way of evaluating CUD within this sample, and the cross-sectional nature of the study limits our ability to derive any conclusions regarding symptomatic change with CMP use. Even though respondents endorsed moderate symptoms we cannot preclude the possibility of improvement in that their symptoms may have been more severe prior to beginning treatment with CMP. Despite many respondents reporting increased cannabis use since receiving CMP authorization and many endorsing daily use, symptoms indicating problematic cannabis use

(social impairment and difficulty controlling use) were minimal. However, data from the National Survey of Drug Use and Health (NSDUH) has suggested that up to 11% of individuals using CMP meet criteria for DSM-IV cannabis abuse/dependence (Lin et al., 2016). Further, daily use is more frequent in medical cannabis users (33%) compared to recreational users (11%) (Lin et al., 2016). We cannot preclude cannabis use disorder (CUD) in our sample as it was not directly examined, however many respondents reported increased use of cannabis since obtaining a prescription. This may suggest the development of tolerance, a hallmark symptom of CUD. The recently published Lower-Risk Cannabis Use Guidelines (LRCUG) (Fischer et al., 2017) suggest frequency or intensity of use to be the strongest and most consistent predictors of severe and/or long-term cannabis-related health problems. However, these guidelines are not specific to medicinal use as there is no existing data to suggest that daily medicinal cannabis use increases risk of CUD. These data highlight the need for additional research to appropriately characterize patients that may benefit from CMP use while protecting those that may be at-risk to possible negative effects.

Of note, many respondents to our survey reported replacing a prescription medication with CMP, primarily antidepressants. A recent US study revealed that 71.8% of their sample of chronic pain medicinal cannabis users decreased use of anti-anxiety medications (benzodiazepines), and to lesser extent antidepressants (37.6%) while using medical cannabis (Piper et al., 2017). Given the high rates of CMP prescription seen for mental health conditions and lack of literature examining the efficacy of CMP in these conditions (NASEM, 2017; Turna et al., 2017), there is an imminent need to begin developing a systematic body of research examining CMP in these conditions. Future studies should examine both the efficacy of cannabis for mental health conditions, as well as its equivalence to current, evidence-based pharmacological treatments. These studies will be critical to inform the development of treatment guidelines so that physicians may prescribe cannabis treatments to patients in an evidence-based and informed manner.

As with any cross-sectional online survey, there are several limitations inherent to the study design. All responses were self-report and retrospective in nature. Although we utilized validated and reliable symptom severity scales to examine prevalence and severity of a given disorder, these do not replace physician confirmation of anxiety and mood disorders. Nevertheless, given that these individuals are physician-authorized CMP users for primarily mental health conditions, it is likely that a medical diagnosis was made by their prescribing physician. We may have a potentially unrepresentative sample as the study was open to self-selection and non-response biases; although the submission of multiple surveys from one participant was prevented, as a verified user number was required. Further participation was incentivized which may have produced additional biases and the number of survey respondents capped. In addition, due to limitations inherent in the cross-sectional design, we were unable to answer several important questions including the impact of potential confounders such as non-psychiatric comorbidity or how many respondents developed anxiety or depression after beginning use of recreational cannabis or CMP. Further, only 25 of 888 respondents in the ANX group endorsed only anxiety and depression and no non-psychiatric condition, limiting the generalizability of these findings. In light of these limitations, the presented findings should be interpreted cautiously and highlight the importance of additional studies to replicate findings in samples of CMP users.

Nevertheless, the results of this study show that patients and physicians are pursuing CMP for a variety of medical conditions including anxiety and a need to inform the significant gaps currently plaguing the existing literature is evident. This research highlights the importance of future studies to clarify the role of cannabis in the treatment landscape. For instance, cannabis is thought to be safe, but it is unclear whether regular use as an anxiolytic treatment poses additional risks. Further, the abuse liability of cannabis is an issue warranting further

consideration, as symptoms of tolerance and withdrawal are not well understood, and psychiatric populations may be particularly vulnerable to this potential consequence. CMP use for mental health conditions requires systematic evaluation to examine efficacy and equivalence using rigorously designed studies including, but not limited to double-blind randomized controlled trials. Research informing CMP prescribers will also be critical given that there is limited information to guide physicians on strains, frequency and dose. This raises a time-sensitive public health concern as legalization of recreational cannabis is forthcoming in Canada which may increase the rate of self-medication with cannabis for mental health purposes. With no information to guide CMP use, it is critical that the scientific literature catch up to policy to better inform patients and physicians respectively.

Disclosures

Michael Van Ameringen: Dr. Van Ameringen reports receiving research funding from the Canadian Foundation for Innovation, Hamilton Health Sciences Organization (HAHSO) Innovation Grant, Janssen Canada and Pfizer Canada; speaker's bureau honoraria from Allergan, Lundbeck Canada, Pfizer and Purdue Canada. He serves on the advisory boards for Allergan, Lundbeck Canada, Otsuka, Almatica and Purdue Canada.

Phillipe Lucas is the Vice President, Patient Research and Access for Tilray.

All remaining authors have no disclosures or conflicts of interest to report.

All authors have approved the final article.

Role of funding source

Tilray (sponsor) permitted inclusion of questions related to anxiety, cannabis use and other variables of interest to the McMaster team in Tilray's annual patient survey. Tilray was responsible for the administration of the survey, data collection and providing respondents with a \$10 incentive. The McMaster-based authors did not receive any funding to support creation of the survey, data analysis or preparation of the manuscript and had complete academic freedom in their interpretation of the data. The sponsor is in agreement to submit the article for publication.

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Revista Brasileira de Psiquiatria

RBP Psychiatry

Official Journal of the Brazilian Psychiatric Association

Volume 34 • Supplement 1 • June/2012



ARTICLE

Cannabidiol, a *Cannabis sativa* constituent, as an anxiolytic drug

Alexandre Rafael de Mello Schier,¹ Natalia Pinho de Oliveira Ribeiro,¹
Adriana Cardoso de Oliveira e Silva,^{1,2,4} Jaime Eduardo Cecilio Hallak,^{3,4}
José Alexandre S. Crippa,^{3,4} Antonio E. Nardi,^{1,4} Antonio Waldo Zuardi^{3,4}

¹ Laboratory of Panic and Respiration, Institute of Psychiatry (IPUB), Universidade Federal do Rio de Janeiro (UFRJ), Brazil

² Universidade Federal Fluminense, Brazil

³ Department of Neuroscience and Behavioral Sciences, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Brazil

⁴ Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (National Institute for Translational Medicine; INCT-TM), Brazil

Received on March 2, 2011; accepted on December 18, 2011

DESCRIPTORS

Cannabidiol;
Cannabis sativa;
Anxiolytics;
Anxiety disorders.

Abstract

Objectives: To review and describe studies of the non-psychotomimetic constituent of *Cannabis sativa*, cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action. **Method:** The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO, combining the search terms “cannabidiol and anxiolytic”, “cannabidiol and anxiolytic-like”, and “cannabidiol and anxiety”. The reference lists of the publications included, review articles, and book chapters were handsearched for additional references. Experimental animal and human studies were included, with no time restraints. **Results:** Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder. **Conclusion:** Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

Introduction

Cannabis sativa is the most used drug of abuse worldwide and around 20% of youth use it heavily and regularly around the globe.¹ The main psychoactive component of the plant is Δ^9 -tetrahydrocannabinol (Δ^9 -THC), one of the substances responsible for the psychoactive effects of Cannabis.²⁻⁴

Cannabidiol (CBD) is another abundant compound in *Cannabis sativa*, constituting around 40% of the plant's active substances.⁵ The pharmacological effects of CBD are different and often opposite to those of Δ^9 -THC.⁶ The number of publications on CBD has increased remarkably over the last years and support the view that CBD has a vast array of possible therapeutic effects. Among these possibilities, the anxiolytic and antipsychotic properties of CBD stand out.⁷⁻¹⁰ CBD's anxiolytic effects are apparently similar to those of approved drugs to treat anxiety,¹¹ although its effective doses have not been clearly established and the mechanisms underlying these effects are not fully understood. The low affinity of CBD for cannabinoid neuroreceptors^{12,13} and its agonist properties at 5-HT_{1A} receptors^{14,15} have been repeatedly demonstrated.

Most studies on CBD have been conducted with rodents, but studies with human samples have also provided promising results.^{16,17} Therefore, the aim of this paper is to review the scientific literature on the anxiolytic properties of CBD in animal and in humans.

Method

The articles selected for this review were identified by searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". In addition, the reference lists of the selected articles and relevant literature reviews and book chapters were handsearched for additional references. We included experimental studies with human and animal samples with no time limits. We sought to exclude studies that used smoked Cannabis, as it is not possible to establish the dose, composition, and proportion of the different cannabinoids in this case, besides the great individual variations in the samples enrolled. Finally, we did not include studies using extracts containing both THC and CBD in oral (Cannador®) or oromucosal spray (Sativex®) forms due to the difficulty to establish the effects of CBD alone (Table 1).

Animal studies

The two first articles about the effects of CBD on experimental anxiety were published in journals that were not indexed in the databases used for this review but were located through handsearch in the reference lists of relevant literature. These two investigations showed contradictory results. In one study, no significant effects of high doses of CBD (100 mg/kg) were seen in rats in the Geller-Seifter conflict test.¹⁸ In the other, a low dose of CBD (10 mg/kg) had anxiolytic effects in rats submitted to the conditioned emotional response test.¹⁹

Later studies using the elevated plus maze (EPM) helped to elucidate this contradiction.⁹ The EPM consists of two opposing open arms (50 x 10 cm) and two closed arms

(50 x 10 x 40 cm) that intersect in their central portion. The arms are made of wood and stand 50 cm above the ground. In this study, mice injected with CBD, diazepam or vehicle (no active substances) were placed in the center of the maze facing the closed arms. The time spent and the numbers of entries in the open and closed arms were measured for 10 minutes. The frequency of entries in the open arms of animals receiving CBD presented an inverted U-shaped curve, with significantly higher rates than those observed in animals treated with vehicle, at the doses of 2.5, 5, and 10 mg/kg. The measures of mice treated with CBD 20 mg/kg did not differ from those of controls, suggesting that anxiolytic effects are only present at low doses, which explains the absence of effects with CBD 100 mg/kg reported in 1981.¹⁸ The same inverted U-shaped dose-response curve was obtained with a wider range of doses of CBD in the EPM (Onaivi et al.).²⁰ Furthermore, the same pattern was observed with the direct infusion of CBD in the periaqueductal gray (PAG) of rats tested in the EPM,^{15,21} confirming that anxiolytic effects should only be expected with low doses of CBD.

The mechanisms through which CBD acts to diminish anxiety have been studied in a number of animal models of anxiety using rodents. One of these studies used Vogel's conflict test,²² in which the animal is water-deprived from and placed in a cage with an electrified grid at the bottom through which the animal receives a shock after licking water for a predetermined number of times. Three substances were tested in rats using the following procedure: CBD (2.5, 5 and 10 mg/kg), diazepam, and flumazenil (an antagonist of benzodiazepine receptors), in addition to vehicle (placebo). The tests showed that CBD produced effects consistent with those of diazepam by increasing the number of licks, even if they resulted in punishment. Flumazenil antagonized the anxiolytic effect of diazepam, but not that of CBD, suggesting that the effects of CBD are not mediated by the activation of benzodiazepine receptors.

There is strong evidence showing that the serotonergic system is involved in the anxiolytic action of CBD. The injection of the 5-HT_{1A} receptor antagonist WAY-100635 (WAY) directly into the dorsolateral portion of the PAG (dIPAG) in rats antagonized the anxiolytic effects of CBD in the EPM and in Vogel's conflict test.¹⁵ The participation of 5-HT_{1A} receptors in the anxiolytic action of CBD was also derived from behavioral and cardiovascular responses to restraint stress in rats.¹¹ In this study, animals were intraperitoneally injected with vehicle or CBD (1, 10 and 20 mg/kg) and, after 30 minutes, they were restrained for 60 minutes. Immobilization increased blood pressure, heart rate, and anxiety responses in the EPM 24 hours later, and these effects were attenuated by CBD. Pretreatment with WAY blocked the anxiolytic action of CBD. The injection of CBD into the intra-dorsal PAG also blocked panic-like responses in the elevated T-maze (ETM) and flight responses to the electrical stimulation of this area.²³ The ETM has three arms with the same dimensions, two open and one closed, and allows the measure of entrance avoidance in the open arms when the animal is placed in the closed arm, as well as of escape when the animal is placed in the open arm. The panic-like response seen with CBD in the two procedures was antagonized by the previous intra-dIPAG administration of WAY.²² Chronic oral administration of CBD also had anti-panic effects in the ETM that were neutralized

Table 1 Studies of the anxiolytic effect of cannabidiol in humans and animals

Study	Model	Route	Dose	Anxiolytic effect
<i>Animals</i>				
Silveira Filho et al. ¹⁸	Conflict test	Intraperitoneal	100 mg/kg	-
Zuardi et al. ¹⁹	Conditioned emotional response paradigm	Intraperitoneal	10 mg/kg	+
Onaivi et al. ²⁰	Elevated plus maze test	Intraperitoneal	0.01, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 50.0 and 100.0 mg/kg	+
Guimarães et al. ⁹	Elevated plus maze test	Intraperitoneal	2.5, 5.0, 10.0 and 20.0 mg/kg	+
Moreira et al. ²²	Vogel's conflict test	Intraperitoneal	2.5, 5.0 and 10.0 mg/kg	+
Resstel et al. ¹⁰	Contextual fear conditioning	Intraperitoneal	10 mg/kg	+
Campos et al. ¹⁵	Elevated plus maze test and Vogel's conflict test	Intra-dorsal periaqueductal gray		+
Bitencourt et al. ²⁸	Contextual fear conditioning	i.c.v.	2.0 microg/microl	+
Campos et al. ²¹	Elevated plus maze test	Intra-dorsal periaqueductal gray	30 or 60 nmol	+
Resstel et al. ¹⁹	Restraint stress	Intraperitoneal	1, 10 and 20 mg/kg	+
Soares et al. ²³	Elevated T maze	Intra-dorsal periaqueductal gray	15, 30 or 60 nmol	+
Lemos et al. ²⁹	Contextual fear conditioning	Intraperitoneal and direct microinjection into the PL prefrontal cortex	10 mg/kg (i.p.) and 30 nmol (microinjection into the PL prefrontal cortex)	+
Casarotto et al. ²⁶	Marble-burying test	Intraperitoneal	15, 30 and 60 mg/kg	+
Gomes et al. ³⁰	Vogel's conflict test	Intra bed nucleus of the stria terminalis	15, 30, and 60 nmol	+
Deiana et al. ²⁷	Marble-burying test	Intraperitoneal and oral	120 mg/kg	+
Uribe-Mariño et al. ³¹	Prey-predator paradigm	Intraperitoneal	0.3, 3.0 and 30 mg/kg	+
Campos et al. ²⁴	Elevated T maze	Oral		+
<i>Humans</i>				
Zuardi et al. ⁷	Decreased STAI scores elevation induced by THC (healthy volunteers)	Oral	1 mg/kg	+
Zuardi et al. ³²	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	Oral	300 mg	+
Crippa et al. ³⁴	Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)	Oral	400 mg	+
Fusar-Poli et al. ³⁵	Decreased skin conductance fluctuation in task with fearful faces during a fMRI procedure (healthy volunteers)	Oral	600 mg	+
Crippa et al. ¹⁷	Decreased VAS factor anxiety scores before SPECT procedure (social phobia patients)	Oral	400 mg	+
Bergamaschi et al. ³³	Decreased VAS factor anxiety scores after public speaking (social phobia patients)	Oral	600 mg	+

by intra-dIPAG injection of WAY. However, chronic administration of CBD did not change the extracellular concentration of serotonin in the dIPAG or the expression of 5-HT1A or 5-HT2C, indicating that CBD directly activates 5-HT1A receptors.²⁴ CBD was also found to activate the vanilloid receptor type 1 (TRPV1)²⁵ and there is evidence that this activation could explain the inverted U-shaped dose-response curve of CBD's anxiolytic effect seen in the EPM. TRPV1 receptors regulate the release of glutamate in the dIPAG and the increased activation of this system would result in increased anxiety. Thus, it has been suggested that elevated doses of CBD in the dIPAG could activate local TRPV1 receptors facilitating the glutamatergic neurotransmission and increasing anxiety.

To test this hypothesis, rats pre-treated with the TRPV1 antagonist capsazepine in the dIPAG were injected with CBD (30 and 60 mg/kg) in the same region and tested in the EPM. The dose of 60 mg/kg CBD, which had no anxiolytic action before, was able to reduce anxiety after pre-treatment with capsazepine, suggesting that the activation of TRPV1 receptors by the higher dose of CBD would counterbalance the anxiolytic effect of CBD produced by the activation of 5-HT1A receptors.²¹

Because serotonin has also been implicated in obsessive-compulsive disorder (OCD), the effects of CBD were tested in mice submitted to the marble-burying test (MBT), an animal model of compulsive behavior. CBD induced a significant reduction in the number of buried marbles at different doses (15, 30, and 60 mg/kg) compared to controls in a dose-dependent pattern. The same was found with the administration of the ISRS paroxetine (10 mg/kg) and diazepam (2.5 mg/kg). However, the effects of CBD 30 mg/kg persisted even after seven days of repeated daily administration, whereas the effects of diazepam disappeared. Pre-treatment with WAY (3 mg/kg) counteracted the effects of paroxetine, but did not affect the action of CBD, which was prevented by pre-treatment with the CB1 receptor antagonist AM251 (1 mg/kg).²⁶ This action of CBD in the MBT was recently replicated by another group using a higher dose (120 mg/kg).²⁷

The participation of specific cannabinoid receptors (CB1) in the anxiolytic action of CBD has also been investigated using animal models. In the study with the EPM that reported the antagonism of the anxiolytic effect of intra-dIPAG CBD by WAY, the CB1 receptor antagonist AM251 was unable to avoid this effect.¹⁵ However, this receptor system seems to be involved in another anxiolytic-like action of CBD, according to tests using a procedure known as contextual fear conditioning. In this procedure, animals are pre-conditioned to a hostile environment (foot shocks) and later exposed to the same environment, when they normally present freezing, the duration of which can be monitored as a measure of anxiety. Both CBD and diazepam are successful in attenuating freezing in rats, as well as the increased heart rate and blood pressure induced by re-exposure to the contextually feared environment.¹⁰ This effect of CBD on contextual memory is also produced by the endocannabinoid reuptake inhibitor AM404, which increases the availability of cannabinoids in the synaptic cleft.²⁸ In this study, the two drugs were injected into the ventricles and their effects were counteracted by the CB1 receptor antagonist SR141716A, suggesting the involvement of the endocannabinoid system in the anxiolytic action of CBD in this model. The pre-limbic region of the prefrontal cortex

appears to underlie this effect of CBD, as the reduction in contextual fear produced by systemic administration of CBD (10 mg/kg) is associated with reduced c-Fos expression in this area. In addition, the microinjection of CBD (30 nmol) in the pre-limbic region of the frontal cortex reduced freezing induced by re-exposure to the aversive context.²⁹ The effects of CBD on contextual fear indicate a possible therapeutic action of this cannabinoid in post-traumatic stress disorder.

Another area that is apparently involved in the anxiolytic-like effects of CBD is the bed nucleus of the stria terminalis (BNST). The intra-BNST injection of CBD (15, 30, and 60 nmol) increased the number of punished licks in Vogel's conflict test and the number of open arm entries in the EPM. These effects were blocked in rats pre-treated with WAY.³⁰

CBD was also effective in an ethologic model that investigates behaviors induced by innate fear, the predator-prey paradigm.³¹ This procedure was performed using a semi-transparent plexiglass box in the shape of a quadrangular arena (154x72x64 cm) with walls covered with a light-reflecting film and floor in transparent plexiglass over a board of stainless steel divided in 20 equal rectangles. One of the corners of the arena has a shelter box with black walls and a complex maze inside. Three days prior to the experiment, the mice were placed and kept in this arena, with free access to food and water until the day of the trial. The "no threat" group had its behaviors recorded for five minutes. Animals exposed to the predator (snake) were divided into four groups (n = 12/11 per group) and pre-treated with intraperitoneal injections of CBD (0.3, 3 and 30 mg/kg) or vehicle (control group). The group of animals that were not confronted with the predator presented no defensive behaviors. Animals pre-treated with CBD had significant reductions in explosive flight and defensive immobility, responses related to panic models. Risk assessment and defensive attention were unaltered in animals treated with CBD. These results suggest that CBD can be effective in the control of panic attacks.

Human studies

The first evidence of CBD's anxiolytic effects in humans, documented with assessment scales, was published in 1982 in a study on the interaction between CBD and THC.⁷ The study sample consisted of eight volunteers with a mean age of 27 years, no health problems and who had not used *Cannabis sativa* in the previous 15 days. In a double-blind procedure, the volunteers received CBD, THC, THC + CBD, diazepam, and placebo in different sequences and days. The results showed that the increased anxiety following the administration of THC was significantly attenuated with the simultaneous administration of CBD (THC + CBD).

Based on this preliminary evidence, researchers decided to investigate a possible anxiolytic action of CBD in experimentally induced anxiety in healthy volunteers using the simulated public speaking (SPS) model.³² The procedure consists of asking a subject to speak in front of a video camera for a few minutes, while subjective anxiety is measured with self-rated scales and physiological correlates of anxiety are recorded (heart rate, blood pressure, skin conductance). CBD (300 mg), as well as the anxiolytic drugs diazepam (10 mg) and ipsapirone (5 mg), administered in a double-blind design, significantly attenuated SPS-induced anxiety.

The SPS test may be regarded as a good model of anxiety and has apparent validity for social anxiety disorder (SAD), as the fear of speaking in public is considered a central feature in this condition. Therefore, the anxiolytic effect of CBD in healthy volunteers observed in this test led to the hypothesis that this cannabinoid could be effective to treat SAD. This hypothesis was recently tested in 24 patients with SAD who had their performance in the SPS test compared to that of a group of 12 healthy controls.³³ The patients with SAD were divided into two groups of 12, one of which received CBD 600 mg and the other placebo, in a double-blind procedure. The results showed that the levels of anxiety, somatic symptoms, and negative self-assessment were higher in patients who took placebo than in those of the CBD group who performed similarly to healthy controls in some measures.

In another study that investigated the effects of CBD on regional cerebral blood flow (rCBF) in healthy volunteers using single photon emission computed tomography (SPECT), SPS-induced anxiety was reduced in patients receiving CBD.³⁴ In that study, patients received either CBD (400 mg) or placebo, in a crossed double-blind design, in two experimental sessions with an interval of one week. CBD significantly reduced subjective anxiety as measured by rating scales, while brain activity was increased in the left parahippocampal gyrus and decreased in the left amygdala-hippocampus complex, including the fusiform gyrus. This pattern of SPECT results is compatible with an anxiolytic action.

SPECT was also used later to investigate the neural correlates of CBD's anxiolytic effects in a sample of patients with SAD.¹⁷ A single dose of CBD 400 mg was able to reduce subjective anxiety measures and SPECT showed changes in the same regions previously identified in healthy volunteers.

Functional magnetic resonance imaging (fMRI), which allows the acquisition of larger series of images with better temporal and spatial resolution, was used to investigate the neural correlates of the anxiolytic effects of CBD in 15 healthy volunteers.³⁵ This experiment showed that CBD (600 mg) attenuated fMRI responses during the recognition of fearful facial expressions in the amygdala and the anterior cingulate, and that this attenuation pattern correlated with skin conductance responses to the stimuli. The same group also reported that the anxiolytic action of CBD occurs by altering the subcortical prefrontal connectivity via amygdala and anterior cingulate.¹⁶

Conclusion

Together, the results from laboratory animals, healthy volunteers, and patients with anxiety disorders support the proposition of CBD as a new drug with anxiolytic properties. Because it has no psychoactive effects and does not affect cognition; has an adequate safety profile, good tolerability, positive results in trials with humans, and a broad spectrum of pharmacological actions,³⁶ CBD appears to be the cannabinoid compound that is closer to have its preliminary findings in anxiety translated into clinical practice.³⁷ Future studies should test this possibility in clinical trials involving patients with different anxiety disorders, especially panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorder. In addition, because the actions of CBD are biphasic, the adequate therapeutic window for each anxiety disorder remains to be determined.

Regarding the mechanism underlying the anxiolytic effects of CBD, the most consistent evidence points to the involvement of the serotonergic system, probably through direct action on 5-HT_{1A} receptors, although other systems, as the endocannabinoid system itself, may also be implicated. Further investigation is warranted to clarify these issues, especially if we consider that CBD is a drug with a variety of effects in the nervous system.³⁸⁻⁴⁰

Disclosures

Alexandre Rafael de Mello Schier

Employment: *Universidade Federal do Rio de Janeiro (UFRJ), Brazil.* Research grant: *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq)*, Brazil.* Other: *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ), Brazil.*

Natalia Pinho de Oliveira Ribeiro

Employment: *Universidade Federal do Rio de Janeiro (UFRJ), Brazil.* Research grant: *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes)*, Brazil.* Other: *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ), Brazil.*

Adriana Cardoso de Oliveira e Silva

Employment: *Universidade Federal Fluminense (UFF), Brazil.* Other: *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ); National Institute for Translational Medicine (INCT-TM), Brazil.*

Jaime Eduardo Cecílio Hallak

Employment: *Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil.* Research grant: *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil.* Other: *THC-Pharm, Novartis, AstraZeneca; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.*

José Alexandre S. Crippa

Employment: *Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil.* Research grant: *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil.* Other: *THC-Pharm, Elli-Lilly, Servier; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.*

Antonio E. Nardi

Employment: *Universidade Federal do Rio de Janeiro (UFRJ), Brazil.* Research grant: *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq)**, Brazil.* Speaker's honoraria: *Glaxo-Smiskline*, Roche.* Consultant/ Advisory board: *Aché*.* Other: *ArtMed*; Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ); National Institute for Translational Medicine (INCT-TM), Brazil.*

Antonio Waldo Zuardi

Employment: *Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil.* Research grant: *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil.* Other: *THC-Pharm; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.*

* Modest

** Significant

*** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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The Endocannabinoid System and the Brain

Raphael Mechoulam¹ and Linda A. Parker²

¹Institute for Drug Research, Hebrew University, Medical Faculty, Jerusalem 91120, Israel; email: mechou@cc.huji.ac.il

²Department of Psychology and Collaborative Neuroscience Program, University of Guelph, Guelph, Ontario N1G 2W1, Canada; email: parkerl@uoguelph.ca

Annu. Rev. Psychol. 2013. 64:21–47

First published online as a Review in Advance on July 12, 2012

The *Annual Review of Psychology* is online at psych.annualreviews.org

This article's doi:
10.1146/annurev-psych-113011-143739

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Keywords

Δ^9 -tetrahydrocannabinol (THC), anandamide, anxiety, 2-arachidonoyl glycerol (2-AG), cannabidiol, cannabinoid receptors, cognition, depression, memory, neurogenesis, reward

Abstract

The psychoactive constituent in cannabis, Δ^9 -tetrahydrocannabinol (THC), was isolated in the mid-1960s, but the cannabinoid receptors, CB1 and CB2, and the major endogenous cannabinoids (anandamide and 2-arachidonoyl glycerol) were identified only 20 to 25 years later. The cannabinoid system affects both central nervous system (CNS) and peripheral processes. In this review, we have tried to summarize research—with an emphasis on recent publications—on the actions of the endocannabinoid system on anxiety, depression, neurogenesis, reward, cognition, learning, and memory. The effects are at times biphasic—lower doses causing effects opposite to those seen at high doses. Recently, numerous endocannabinoid-like compounds have been identified in the brain. Only a few have been investigated for their CNS activity, and future investigations on their action may throw light on a wide spectrum of brain functions.

Contents

INTRODUCTION: CANNABIS AND THE BRAIN	22
Cannabis Use Over Millennia: A Bird’s-Eye View	22
Δ^9 -Tetrahydrocannabinol and Cannabidiol	23
The Endocannabinoid Receptors ...	24
The CB1 Receptor	24
The CB2 Receptor	25
Endogenous Cannabinoid Agonists .	26
THE CANNABINOID SYSTEM IN ANXIETY AND DEPRESSION ..	27
Endocannabinoids and Anxiety	27
The Endocannabinoid System, Neurogenesis, and Depression ...	29
CANNABINOIDS AND REWARD SYSTEMS	30
Rewarding/Aversive Effects of Cannabinoids	30
Cannabinoids and Relapse	31
CANNABINOIDS AND COGNITION	33
Effects of Cannabis on Cognition in Humans	33
Effects of CB1 Agonists on Learning and Memory in Nonhumans	34
Effects of CB1 Antagonists on Learning and Memory in Nonhumans	35
Role of Endocannabinoids in the Hippocampus in Learning and Memory	35
Endocannabinoid Modulation of Extinction of Aversive Memory ..	36
CONCLUSIONS	37

INTRODUCTION: CANNABIS AND THE BRAIN

Cannabis Use Over Millennia: A Bird’s-Eye View

The Assyrians (about second millennium BC to sixth century BC) used cannabis for its

psychoactive, mind-altering effects as well as for its medical properties. It was named either *ganzi-gun-nu* (“the drug that takes away the mind”) or *azzalu*, which was apparently a drug for “depression of spirits,” for a female ailment (possibly amenorrhea), or even for annulment of witchcraft (Campbell Thomson 1949). The importance of cannabis intoxication seems to have been central in early Zoroastrian shamanic ecstasy (Mechoulam 1986). Its wide use in the Middle East has continued ever since. Indeed, it was a central theme in Arab poetry of the Middle Ages (Rosenthal 1971). In China and India it was known for the dual nature of its effects. In the Chinese classic medical pharmacopeia Ben Ts’ao, originally compiled around the first century AD, cannabis was recommended for numerous maladies, “but when taken in excess it could cause seeing devils” (Mechoulam 1986, p. 9).

In Europe, cannabis was introduced by the Napoleonic soldiers returning from Egypt and by British physicians returning from India. Industrial hemp, which contains negligible amounts of psychoactive material, was of course grown previously, but the psychoactive variety was unknown. The psychological effects caused by cannabis preparations—presumably North African hashish—became known in Europe mostly through the writings of members of the Parisian *Le Club des Hashichins* in the mid-nineteenth century, particularly Baudelaire, Gautier, and Moreau (Mechoulam 1986). Baudelaire, a major literary figure at the time, emphasized the “groundless gaiety” and “the distortion of sounds and colours” following cannabis use. Moreau, a psychiatrist, in his 1845 book, *Hashish and Mental Illness* (Moreau 1973), described in detail numerous psychological phenomenon noted in experimental subjects: feeling of happiness, excitement and dissociation of ideas, errors of time and space, enhancement of the sense of hearing, delusions, fluctuations of emotions, irresistible impulses, and illusions and hallucinations. This diversity of actions—some of them opposite to each other—has confounded cannabis research ever since. Indeed, Moreau reported that some of

his volunteers experienced "...occurrences of delirium or of actual madness". He concluded, "There is not a single, elementary manifestation of mental illness that cannot be found in the mental changes caused by hashish..." (Moreau 1973, p. 18). But today few marijuana users will reach a state of "delirium or of actual madness." In most cases, they will report an increase in relaxation and euphoria and possibly enhancement of their senses, but an impairment of memory. These striking differences are probably due to the well-known biphasic activity of Δ^9 -tetrahydrocannabinol (THC)—the psychoactive constituent—whose effects at low doses may be opposite to those produced by high doses. Moreau's volunteers presumably orally consumed large amounts of hashish, whereas today North Americans and Europeans usually smoke cannabis, and most users adjust their dose to achieve the desired effects.

Surprisingly, research on cannabis advanced slowly. A major reason for the neglect was the lack of knowledge of its basic chemistry. Modern research—namely research over the past 150 years—is based on quantitative data. Unlike morphine and cocaine, which had been isolated and made available in the nineteenth century and thus could be quantitatively investigated *in vitro*, in animals, and in humans, the psychoactive constituent(s) of cannabis were not isolated and their structures were not elucidated until the 1960s; hence quantitative research was not possible before then.

It is conceivable that the material reaching Europe in the past varied widely in its contents; thus its medical use also was not reliable, and research with it was of little value. Indeed, around the beginning of the twentieth century cannabis almost disappeared, both as a medicinal agent and for recreational purposes in Europe and in North America. In addition, the anti-cannabis laws made research on it, particularly in academic institutions, very difficult. Indeed, from the early 1940s until the mid-1960s, research on cannabis was limited to a few scattered groups. This paucity of early research has now been more than compensated for by the avalanche of papers on the plant cannabi-

noids and on the endogenous cannabinoids. Not surprisingly, the burst of recreational marijuana use, in the mid-1960s in the United States and later in Europe, coincided with the new wave of research on cannabis.

Δ^9 -Tetrahydrocannabinol and Cannabidiol

Over nearly a century, numerous attempts were made to isolate in pure form the active marijuana constituent(s) and to elucidate its (or their) structure(s), but these attempts were unsuccessful (Mechoulam & Hanus 2000). Now we can understand the reason for this lack of success. There are more than 60 cannabis constituents, with closely related structures and physical properties, making their separation difficult. With the advance of modern separation techniques, the isolation and the structure elucidation of the active principle, THC, was finally achieved in 1964 (Gaoni & Mechoulam 1964). Shortly thereafter, THC was synthesized (Mechoulam et al. 1967). Thus, THC became widely available for research, and several thousand papers have been published on it. Surprisingly, although most of the plant cannabinoids have now been identified—and their structures are related chemically—the only major mood-altering constituent is THC.

Another major plant cannabinoid is cannabidiol (CBD), which was isolated during the late 1930s, but its structure was elucidated only in 1963 (Mechoulam & Shvo 1963). As it does not parallel THC in its central nervous system (CNS) effects, initially only a limited amount of research was focused on it. However, over the past two decades CBD was found to be a potent anti-inflammatory agent, to attenuate the memory-impairing effects produced by THC, and to cause a plethora of other effects. Hundreds of publications have addressed its various actions (for a review, see Mechoulam et al. 2009). Both THC and CBD are present in the plant mainly as their nonpsychoactive carboxylic precursors (THC-acid and CBD-acid), which slowly lose their acidic function (decarboxylate) in the

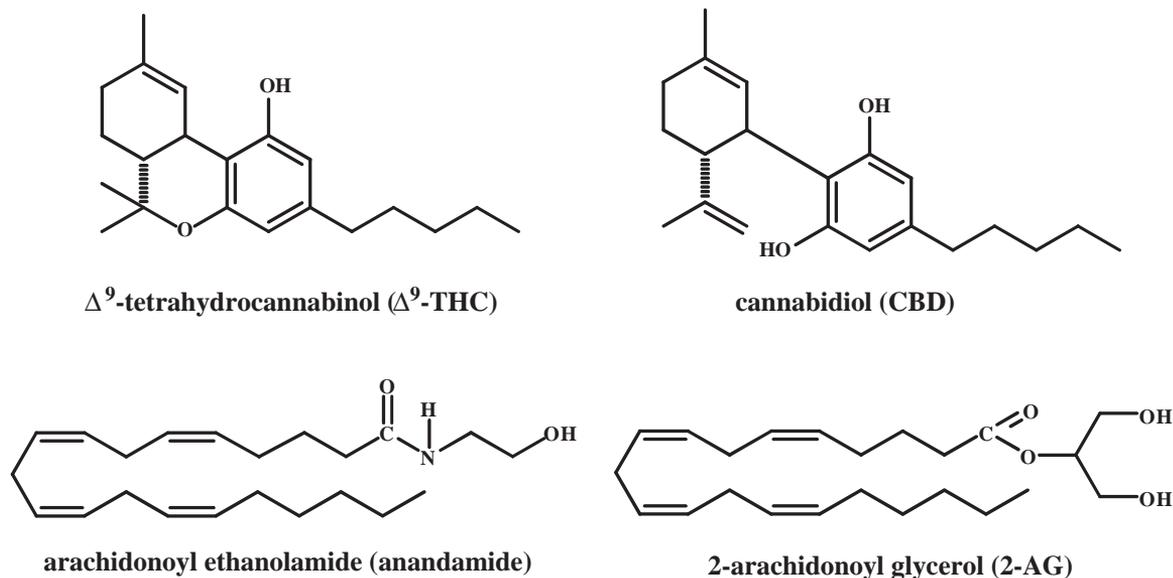


Figure 1

Structures of the plant cannabinoids Δ⁹-tetrahydrocannabinol and cannabidiol and of the endogenous cannabinoids anandamide and 2-arachidonoyl glycerol.

plant on heating. The structures of THC and CBD are presented in **Figure 1**.

The cannabis plant varieties differ tremendously in their contents. In industrial hemp the concentration of THC is less than 0.3%, in hashish in the 1960s it was about 5%, whereas in marijuana it was about 2% to 3%, but nowadays strains have been developed—mostly for illegal use—that contain up to 25%.

The Endocannabinoid Receptors

Originally it was assumed that cannabinoids act through a nonspecific membrane-associated mechanism; however, the very high stereospecificity of the action of some synthetic cannabinoids pointed to a more specific mechanism (Mechoulam et al. 1988). The first data indicating that cannabinoids may act through receptors were published by Howlett, who showed that cannabinoids inhibit adenylate cyclase formation, and the potency of the cannabinoids examined paralleled the level of their pharmacological action (Howlett et al. 1986). The same group shortly thereafter indeed

reported the existence of binding sites in the brain (Devane et al. 1988). Their distribution was found to be consistent with the pharmacological properties of psychotropic cannabinoids (Herkenham et al. 1990), and the receptor was cloned (Matsuda et al. 1990). A second, peripheral receptor, CB₂, was later identified in the spleen (Munro et al. 1993). Both CB₁ and CB₂ receptors belong to the superfamily of G protein-coupled receptors (GPCRs). The two cannabinoid receptors exhibit 48% amino acid sequence identity. Both receptor types are coupled through G proteins to adenylyl cyclase and mitogen-activated protein kinase (for a detailed review on the pharmacology of cannabinoids, see Howlett et al. 2002).

The CB₁ Receptor

It was originally believed that the CB₁ receptor was expressed mainly in the CNS, and hence it was considered a brain cannabinoid receptor. We are now aware that it is present in numerous peripheral organs, although in some of them the receptor levels are low. CB₁ receptors are

among the most abundant GPCRs in the brain. The highest densities of CB1 receptors, in the rodent brain, are noted in the basal ganglia, substantia nigra, globus pallidus, cerebellum, and hippocampus, but not in the brainstem. The high CB1 levels in the sensory and motor regions are consistent with the important role of CB1 receptors in motivation and cognition. CB1 receptors appear to be involved in γ -aminobutyric acid (GABA) and glutamate neurotransmission, as they are found on GABAergic and glutamatergic neurons (Howlett et al. 2002). The CB1 receptor is present and active from the earliest phases of ontogenetic development, including during the embryonal stages, which indicates that it is of importance in neuronal development and newborn suckling (Fride et al. 2009). Surprisingly the CB1 receptor levels in rats are increased on transition from adolescence [postnatal days (PND) 35–37] to adulthood (PND 70–72), a pattern that is opposite to that of other neuroreceptor systems (Verdurand et al. 2012). Also, unexpectedly, ligands that interact similarly with CB1 receptors may have significantly different pharmacological profiles. This may be due to the ability of CB1 receptors to form heteromeric complexes with other GPCRs (Pertwee et al. 2010).

The distribution of CB1 receptors differs in neonatal brain and adult brain. It is abundant in white matter areas at the early age but is much less abundant later (Romero et al. 1997). It is of interest to determine whether this difference has anything to do with the behavioral landmarks associated with different ages.

The CB1 receptors are found primarily on central and peripheral neurons in the presynapse. These locations facilitate their inhibition of neurotransmitter release, which is one of the major functions of the endocannabinoid system. Activation of CB1 receptors leads to a decrease in cyclic adenosine monophosphate (cAMP) accumulation and hence to inhibition of cAMP-dependent protein kinase (PKA). CB1 receptor activation leads to stimulation of mitogen-activated protein (MAP) kinase activity, which is a mechanism by which cannabinoids affect synaptic plasticity,

cell migration, and possibly neuronal growth (Howlett et al. 2002). CB1 receptors are also coupled, again through G proteins, to several types of calcium and potassium channels.

Several types of CB1 receptor gene knock-out mice are available and are widely used (Zimmer et al. 1999). CB1 receptor gene polymorphisms have been observed, and their importance is yet unknown, although susceptibility to addiction and neuropsychiatric conditions has been suggested (Zhang et al. 2004).

The CB2 Receptor

It was originally assumed that CB2 receptors were present only in cells of the immune system; however, they have now been identified throughout the CNS (Ashton et al. 2006, Onaivi et al. 2008a, van Sickle et al. 2005), particularly in microglial cells (Nunez et al. 2004, Stella 2004), though at lower levels than those of the CB1 receptors. Under some pathological conditions, CB2 receptor expression is enhanced in the CNS as well as in other tissues. It seems possible that the CB2 receptor is part of a general protective system (for a review, see Pacher & Mechoulam 2011). In that review, we speculated that “The mammalian body has a highly developed immune system which guards against continuous invading protein attacks and aims at preventing, attenuating or repairing the inflicted damage. It is conceivable that through evolution analogous biological protective systems have evolved against nonprotein attacks. There is emerging evidence that lipid endocannabinoid signaling through CB2 receptors may represent an example/part of such a protective system” (Pacher & Mechoulam 2011, p. 194). In view of the various protective effects associated with the CB2 receptor, several synthetic CB2-specific receptor agonists, which do not bind to the CB1 receptor, have been synthesized. HU-308 was one of the first such compounds reported (Hanus et al. 1999); however, numerous additional ones are now known, and since they do not cause the psychoactive effects associated with CB1 agonists, several pharmaceutical firms are presently active in the field.

CB2 receptor agonists might be expected to become drugs in various fields, including neuropsychiatric, cardiovascular, and liver disease.

Endogenous Cannabinoid Agonists

The discovery of the cannabinoid receptors suggested that endogenous molecules, which may stimulate (or inhibit) the receptors, are presumably present in the mammalian body. The plant constituent THC, which, apparently by a quirk of nature, binds to these receptors, is a lipid compound; hence it was assumed that any possible endogenous cannabinoid molecules (endocannabinoids) would also be lipids. Indeed, we were able to isolate and identify two compounds, one from brain—which we named anandamide, based on the Sanskrit word *ananda* (“supreme joy”)—and a second one [2-arachidonoyl glycerol (2-AG)] from peripheral tissues (Devane et al. 1992, Mechoulam et al. 1995). Their structures are presented in **Figure 1**. These two endogenous cannabinoids have been investigated in great detail (for a review, see Howlett et al. 2002). Additional endogenous molecules that bind to the cannabinoid receptors have been identified, but some of them may be artifacts, and interest in them is negligible.

Unlike most neurotransmitters (e.g., acetylcholine, dopamine, and serotonin), anandamide and 2-AG are not stored in vesicles but rather are synthesized when and where they are needed. Again, unlike most neurotransmitters, their action is not postsynaptic but rather mostly presynaptic, i.e., they serve as fast retrograde synaptic messengers (Howlett et al. 2002). However, whether both endocannabinoids, or only 2-AG, serve as fast retrograde synaptic messengers remains to be established. Thus 2-AG, after its postsynaptic synthesis, crosses the synapse and activates the cannabinoid presynaptic receptor, which makes possible the inhibition of various neurotransmitter systems that are present there. This is a primary activity of the endocannabinoids.

Contrary to THC, which is metabolized over several hours and excreted (or stored as

one of its metabolites), endocannabinoids are rapidly removed by a membrane transport process yet to be fully characterized (Fu et al. 2011). In the cell, anandamide is hydrolyzed to arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH). 2-AG is also hydrolyzed enzymatically, both by FAAH and by monoacyl hydrolases. Suppression of these enzymes prolongs the activity of the endocannabinoids (Gaetani et al. 2009).

Although there is solid evidence that the activation of presynaptic CB1 receptors can lead to inhibition of the release of a number of different excitatory or inhibitory neurotransmitters both in the brain and in the peripheral nervous system, there is also in vivo evidence that CB1 receptor agonists can stimulate dopamine (DA) release in the nucleus accumbens (Gardner 2005). This effect apparently stems from a cannabinoid receptor-mediated inhibition of glutamate release. Indeed, many of the actions of cannabinoid receptor agonists (including endocannabinoids) are dose-dependently biphasic (Sulcova et al. 1998). Endocannabinoids also exhibit an “entourage effect”—namely enhancement of their activity by structurally related, biologically inactive, endogenous constituents (Ben-Shabat et al. 1988). The multiple functions of endocannabinoid signaling in the brain have recently been very well reviewed (Katona & Freund 2012).

In the following review of the effects of brain endocannabinoids and related fatty acid amides of amino acids (FAAAs) and closely related compounds on emotions and cognition, we summarize the large number of published observations. It seems that many of the FAAAs in the CNS that have been investigated—and most have not been investigated yet—have significant effects. If we assume that the dozens of compounds of this type present in the brain are not biosynthesized by mistake but rather play some physiological role, it is tempting to speculate that their levels and their interactions may be of importance in the profile of emotions and possibly of individual personalities. This topic is further discussed in the Conclusions section of this review.

THE CANNABINOID SYSTEM IN ANXIETY AND DEPRESSION

Freud considered the problem of anxiety a “nodal point, linking up all kinds of most important questions; a riddle, of which the solution must cast a flood of light upon our whole mental life” (Freud 1920). We have made some progress since Freud’s time, but according to the National Institute of Mental Health, anxiety disorders still affect about 40 million people in the United States alone, and anti-anxiety drugs are among the top prescription drugs.

Cannabis has been used for millennia as a medicinal agent (Mechoulam 1986). In India, *bhangue* (the local name for cannabis at the time) was believed to help the user to be “delivered from all worries and care” (Da Orta 1563), and its extensive present-day use throughout the world is presumably due, in part at least, to the same effects. For recent reviews on cannabis and anxiety, see Gaetani et al. (2009), Moreira & Wotjak (2010), Parolaro et al. (2010), and Zanettini et al. (2012). For general reviews on the endocannabinoid system, including detailed data on anxiety and depression and emerging pharmacotherapy, see Pacher et al. (2006) and Pertwee (2009).

A few years ago the major pharmaceutical firm Sanofi-Aventis developed and initiated marketing for an antagonist (or more precisely an inverse agonist) of the CB1 receptor. Because CB1 agonists enhance appetite, such a drug could become a major weapon against obesity. Many other companies had related compounds in various stages of development. The Sanofi compound, named rimonabant, indeed affected obesity and even blocked the psychoactive effects of THC, including short-term memory and lowered cocaine-seeking responses to suitable cues (in animals). However, although psychiatric disorders were indicated as exclusion criteria, rimonabant-treated patients had enhanced anxiety problems and suicidal tendencies (Christensen et al. 2007), and the drug had to be withdrawn from the market. This rather expensive proof is a further addition to previous

evidence, indicating the importance of the CB1 cannabinoid system in anxiety. Interestingly, Lazary et al. (2011) have recently suggested that as some variants of the CB1 receptor gene contribute more significantly than others to the development of anxiety and depression, by genomic screening—possibly in combination with the gene of the serotonin transporter—high-risk individuals could be identified and excluded from the treatment population and thus CB1 antagonists could still be useful. Such screening and treatment would represent a model for modern personalized medicine.

As mentioned previously, many of the psychological effects of cannabis, as well as of THC, are biphasic, depending principally on the dose level and to a certain extent upon the personality of the user. In normal subjects, THC may cause either euphoria and relaxation or dysphoria and anxiety (D’Souza et al. 2004, Wade et al. 2003). Pure THC may not entirely mimic the effects of cannabis, which contains additional cannabinoid constituents, such as CBD, that modulate the effect of THC. Besides, CB1 receptors rapidly desensitize following the administration of agonists, further diminishing the effect of agonists.

Cannabidiol, which does not bind to either CB1 or CB2, possesses anxiolytic and antipsychotic properties (Mechoulam et al. 2002) both in animals and in humans. It shows anxiolytic-like effects with mice in the elevated plus maze and in the Vogel conflict test (Guimarães et al. 1990, Moreira et al. 2006). In humans it was found to lower anxiety in stressful situations (Bergamaschi et al. 2011). The mode of action of CBD as an anxiolytic molecule is not well understood. Most probably it involves action as a serotonin receptor 1A (5-HT_{1A}) agonist (Campos & Guimaraes 2008), enhancement of adenosine signaling through inhibition of uptake (Carrier et al. 2006), or inhibition of the GPR55 receptor (Sharir & Abood 2010).

Endocannabinoids and Anxiety

There are no direct experimental data on the role of endocannabinoids on anxiety in

humans. To our knowledge neither anandamide nor 2-AG has ever been administered to human subjects. This is an absurd situation, presumably a result of regulatory limitations. By contrast, when insulin was discovered in the 1920s, it became an available drug within a year. We can only assume that, because many of the physiological systems are regulated through checks and balances by a variety of endogenous molecules, the endocannabinoids, which affect neurotransmitter release, apparently exert such an action on anxiety, which is a normal human reaction to a variety of stressful conditions.

Considerable data exist on the direct effects of endocannabinoids on anxiety in animals. Rubino et al. (2008) have shown that methanandamide (a stable analog of anandamide) injected into the prefrontal cortex of rats leads to an anxiolytic response. However, large increases of the dose administered led to an anxiogenic response due to TRPV1 stimulation.

An indirect pathway for enhancement of endocannabinoid levels is by blocking their enzymatic hydrolysis. The Piomelli group (Kathuria et al. 2003) reported a novel class of potent, selective, and systemically active carbamate-based inhibitors of FAAH, the enzyme responsible for the degradation of anandamide. The best inhibitors in this series (URB532 and URB597) had anxiolytic properties in rats in the elevated zero-maze test and suppressed isolation-induced vocalizations due to augmented brain levels of anandamide. These effects could be prevented by blockage of the CB1 receptor. These results indirectly confirmed that anandamide has antianxiety properties. The rationale behind this approach is based on the mechanism of anandamide formation and release, which is known to take place when and where needed. As mentioned above, contrary to the classical neurotransmitters, anandamide is not stored in synaptic vesicles but rather is synthesized and released in the synaptic cleft following neuronal activation. Presumably its levels and those of FAAH in anxiety and depression will be highest in the brain areas involved in the regulation of mood and emotions. Therefore, inhibition of anandamide

metabolism would enhance CB1 activation mainly where anandamide levels are highest. Following the same experimental rationale, Moise et al. (2008) confirmed that URB597 inhibited FAAH activity and led to elevated levels of additional fatty acid amides (N-palmitoyl ethanolamine and N-oleoyl ethanolamine), but not of anandamide itself, in hamster brain. However, Cippitelli et al. (2008) have reported an elevation of anandamide levels in rats with URB597, which was found to reduce anxiety associated with alcohol withdrawal. Blockade of the CB1 receptor with rimonabant induced anxiogenic-like behavior in the elevated plus maze; URB597 induced anxiolytic-like effects in this assay. URB597 did not alter unconditioned or conditioned social defeat or rotarod performance.

Enhancement of 2-AG levels produces similar effects. Sciolino et al. (2011) have shown that enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-AG-hydrolyzing enzyme monoacylglycerol lipase (MGL), produces anxiolytic effects under conditions of high environmental aversiveness in rats.

Recently, two parallel publications indicated that the CB2 receptor is also involved in endogenous antianxiolytic activity. García-Gutiérrez & Manzanares (2011) reported that mice overexpressing the CB2 receptor showed lower anxiety-like behaviors in the open field, the light-dark box, and the elevated plus maze tests, indicating that increased expression of the CB2 receptor significantly modifies the response to stress in these tests. Busquets-García et al. (2011), using doses of URB597 and JZL184 that selectively modulated the concentrations of anandamide and 2-AG, respectively, recorded similar anxiolytic-like effects in two behavioral paradigms. However, whereas the anxiolytic-like effects of URB597 were mediated through a CB1-dependent mechanism, the anxiolytic-like effects of JZL184 were CB1 independent. The anxiolytic-like effects of JZL184 were absent in CB2 knockout mice and were prevented by pretreatment with selective CB2 antagonists. These two

publications indicate the crucial role of the CB2 receptor on the modulation of anxiety. As activation of the CB2 receptor does not lead to undesirable psychoactivity, these observations may be of significant clinical importance, and therefore the CB2 receptor represents a novel target to modulate anxiety-like responses. The protective effect of the CB2 receptor is in line with our previous suggestion that this receptor is part of a general protective mechanism (Pacher & Mechoulam 2011).

The molecular mechanism of the effect of endocannabinoids on anxiety is still to be fully clarified. Andó et al. (2012) have confirmed considerable involvement of CB1 receptors in the effect of exo- and endocannabinoids on GABA efflux. However, they also found that CB2-like receptors are likely involved. Hofmann et al. (2011) have described a new form of cannabinoid-mediated modulation of synaptic transmission, so far in the dentate gyrus only. They report that anandamide action under certain conditions is not mediated by CB1 receptors, CB2 receptors, or vanilloid type I receptors, and is still present in CB1^{-/-} animals. It would be of interest to determine whether this new pathway (through a receptor?) is involved in anxiety and depression.

The endocannabinoid system plays a gatekeeper role with regard to activation of the hormonal hypothalamic-pituitary-adrenal (HPA) axis. Tonic endocannabinoid signaling constrains HPA axis activity, ultimately habituating the stress response and restoring homeostasis. Specifically, glucocorticoids produced in response to stress recruit endocannabinoids to increase the excitability of principal neurons in the prelimbic region of the medial prefrontal cortex; the principal neurons initiate inhibitory relays terminating HPA axis activation (Hill et al. 2011). However, following chronic stress, endocannabinoid signaling downregulation is implicated in the overload of hormonal signaling that can result in anxiety and depression in humans. For an excellent review of this literature, see Riebe & Wotjak (2011).

The Endocannabinoid System, Neurogenesis, and Depression

Hill et al. (2008) have summarized the results of the experimental work done on the endocannabinoid system and depression and have concluded that research so far supports the assumption that hypofunctional endocannabinoid signaling contributes to depressive illness and that enhanced endocannabinoid signaling is associated with antidepressant efficacy. However, a hyperfunctional endocannabinoid system contributes to depression. This discrepancy was explained by showing that in the animal model of depression that was used, endocannabinoid signaling was differentially altered in various brain areas. The antidepressive drug imipramine affected some, though not all, of these changes.

In view of the excellent existing summary by Hill et al. (2008), in the present review we discuss mainly the relation between cannabinoids, their two known receptors, and neurogenesis. A leading current hypothesis of depression is that it is linked with neurogenesis. This hypothesis is based on the downregulation of neurogenesis in depressive-like behaviors in animals and on its upregulation by antidepressant treatments.

Over the past few years, considerable data have indicated that the endocannabinoid system plays a central role in neurogenesis (for reviews, see Galve-Roperh et al. 2009, Oudin et al. 2011). It is established that CB1 mRNA is expressed in many regions of the developing brain (Buckley et al. 1998), activation of CB1 is required for the axonal growth response (Williams et al. 2003), the endocannabinoid system drives neural progenitor cell proliferation (Aguado et al. 2006), and cannabinoids actually promote neurogenesis (Berghuis et al. 2007). Reductions in adult neurogenesis were noted in CB1- and CB2-knockout mice (Aguado et al. 2006, Palazuelos et al. 2006). Jin et al. (2004) have reported that both CB1 and VR1 receptors are involved in adult neurogenesis.

Endocannabinoids, particularly 2-AG and diacylglycerol lipases (DAGLs), which are

involved in 2-AG synthesis, play a major role in axonal growth and guidance during development (Oudin et al. 2011). Harkany and colleagues (Keimpema et al. 2010) have shown that the synthesizing enzymes (the DAGLs) alone are not sufficient to account for the growth effect of 2-AG, but both the DAGLs and the degradation enzyme, MGL, play a role. However, MGL is temporally and spatially restricted from the neurite tip, thus enhancing 2-AG activity during axonal growth. The CB2 receptor has recently been shown to promote neural progenitor cell proliferation via mTORC1 signaling (Palazuelos et al. 2012).

Because depression decreases neurogenesis, the findings summarized above are particularly exciting, as they not only help us understand the role of endocannabinoids as endogenous antidepressants but also suggest that synthetic endocannabinoid-like compounds may be developed as a novel type of antidepressive drug.

Onaivi et al. (2008a) and van Sickle et al. (2005) have reported that, contrary to previous reports, CB2 receptors are present in the brain. This unexpected discovery led several groups to investigate the relevance of this receptor in various brain pathological states. Thus, transgenic mice overexpressing the CB2 receptor showed decreased depressive-like behaviors in several relevant assays. Also, contrary to wild-type mice, these transgenic mice showed no changes in BDNF gene and protein expression under stress (García-Gutiérrez et al. 2010). The Onaivi group reported that in Japanese depressed subjects there is high incidence of a certain polymorphism in the CB2 gene (Onaivi et al. 2008b). Hu et al. (2009) compared the antidepressant action of the CB2 agonist GW405833 with the action of desipramine in two antidepressive rodent assays—the time of immobility and a swimming assay. Although both desipramine and GW405833 significantly reduced immobility, contrary to desipramine, GW405833 had no effect in the swimming test. These results indicate that desipramine and cannabinoid drugs have different mechanisms in their antidepressive action.

These results together indicate that as increased CB2 receptor expression reduces depressive-related behaviors, apparently via a mechanism that differs from the mode of action of most antidepressants used at present, the CB2 receptor could be a novel therapeutic target for depression. It will be of interest to establish whether the activity of the CB2 receptor in depression is related to neurogenesis.

CANNABINOIDS AND REWARD SYSTEMS

Although the conditions under which cannabinoid drugs have rewarding effects are more restricted than with other drugs of abuse (such as cocaine and heroin), when they produce reward-related behavior, similar brain structures are involved (for an excellent recent review, see Serrano & Parsons 2011).

Rewarding/Aversive Effects of Cannabinoids

In humans, marijuana produces euphoria, but dysphoria, dizziness, and anxiety are also reported, probably the result of the previously mentioned biphasic effects of THC. Following administration of THC to humans, some studies have shown increased dopamine transmission (Bossong et al. 2009) but others have shown no change in dopamine transmission (Barkus et al. 2011) as measured by positron emission tomography. The endocannabinoid system may play a specific role in appreciation of rewards, as THC pretreatment attenuated the brain response to feedback of monetary rewards as measured by functional magnetic resonance imaging (fMRI) (van Hell et al. 2012).

In animal models, early research suggested that THC was not rewarding to monkeys (Harris et al. 1974) when assessed in the drug self-administration paradigm. In rodents, some investigators have reported that THC (as well as other abused drugs such as cocaine) reduces the threshold for electrical brain stimulation reward (Gardner et al. 1988), but other investigators report that it increases the

threshold (Vlachou et al. 2007). Unlike the self-administration paradigm, the conditioned place preference (CPP) paradigm can be used to assess both the rewarding and the aversive effects of drugs. Conflicting findings were reported in studies using the CPP paradigm with rodents. Early reports revealed that THC produced CPPs (Lepore et al. 1995), but other reports showed conditioned place aversions (e.g., Mallet & Beninger 1998a, Parker & Gillies 1995) due to differing CPP procedures. Indeed, unlike other rewarding drugs, such as cocaine or heroin, low-dose pre-exposure to the effects of THC is necessary to establish a CPP in rodents (Valjent & Maldonado 2000).

More recently, Tanda et al. (2000) have developed a very sensitive and reliable method of establishing self-administration in monkeys, which relies on the use of very low doses of THC but does not require pre-exposure to the drug. In addition, both anandamide (Justinova et al. 2005) and 2-AG (Justinova et al. 2011) are self-administered by monkeys with or without a cannabinoid self-administration history, and both effects are prevented by pretreatment with rimonabant, indicating that the rewarding effect is CB1 receptor mediated. Treatment with the FAAH inhibitor, URB597, shifts the anandamide self-administration dose-response curve to the left, such that anandamide has rewarding effects at lower doses (Justinova et al. 2008). However, URB597 is not self-administered by monkeys (Justinova et al. 2008) and does not produce a CPP in rats (Gobbi et al. 2005), possibly because it neither causes THC-like effects nor increases extracellular mesolimbic DA levels in rats (Justinova et al. 2008, Solinas et al. 2007). In contrast, DA is known to be released in the striatum by THC (Bossong et al. 2009). Cues associated with marijuana use also activate the reward neurocircuitry associated with addiction in humans (Filbey et al. 2009). Indeed, microinjections of THC into the posterior ventral tegmental area (VTA) and into the posterior shell of the nucleus accumbens (NAcc) serve as rewards for both self-administration and CPP in rats (Zangen et al. 2006).

Cannabinoids and Relapse

Treatment of addiction is often hindered by the high rate of relapse following abstinence from the addicting drug. Multiple factors such as exposure to drug-associated stimuli, drug priming, and stress can precipitate drug craving and relapse in humans. In humans, alterations in the CB1 receptor gene and in the FAAH gene have been shown to enhance fMRI activity in reward-related areas of the brain during exposure to marijuana cues (Filbey et al. 2010).

Considerable recent research suggests that CB1 receptor antagonism (or inverse agonism) interferes with drug- and cue-induced relapse in animal models. Relapse is characterized by drug-seeking behavior in extinction triggered by renewed exposure to drug-associated cues or a priming dose of a drug itself (Everitt & Robbins 2005). Such drug-seeking behavior contrasts with actual drug-taking behavior during the self-administration session. Rimonabant prevents drug-associated cues from producing relapse following extinction training in rats and mice (De Vries & Schoffelmeer 2005). Recent evidence suggests that rimonabant is relatively more effective in interfering with drug-seeking behavior than drug-taking behavior (De Vries & Schoffelmeer 2005). In an early report, the CB1 receptor agonist, HU-210, was shown to reinstate cocaine seeking following long-term extinction of cocaine self-administration (De Vries et al. 2001), an effect that was prevented by rimonabant. Of most therapeutic importance, however, was that rimonabant alone blocked drug seeking evoked by the cocaine-paired cues and by a priming injection of cocaine, as well as seeking of heroin (De Vries et al. 2005, Fattore et al. 2003), methamphetamine (Anggadiredja et al. 2004), and nicotine (De Vries et al. 2005) evoked by drug-associated cues and by a priming injection of the drug itself. Therefore, blockade (or inverse agonism) of the CB1 receptor interferes generally with drug-seeking behavior.

Drug-seeking behavior represents the incentive motivational effects of addictive drugs under control of the mesolimbic DA system.

The regulation of the primary rewarding effects of drugs of abuse may be in part controlled by endocannabinoid release in the VTA, which produces inhibition of the release of GABA, thus removing the inhibitory effect of GABA on dopaminergic neurons (Maldonado et al. 2006). In the NAcc, released endocannabinoids act on CB1 receptors on axon terminals of glutamatergic neurons. The resulting reduction in the release of glutamate on GABA neurons that project to the VTA results in disinhibition of the VTA dopamine neurons. Blockade of CB1 receptors attenuates the release of DA in the NAcc in response to rewarding medial forebrain bundle electrical stimulation (Trujillo-Pisanty et al. 2011). The prefrontal cortex and NAcc appear to play a primary role in the prevention of cue-induced reinstatement of heroin (Alvarez-Jaimes et al. 2008) and cocaine (Xi et al. 2006) seeking by CB1 antagonism.

Although blockade of CB1 receptors affects cue- and drug-induced relapse, it does not appear to affect cocaine seeking that is reinstated by exposure to mild footshock stress (De Vries et al. 2001). Indeed, stress-induced relapse to heroin or cocaine seeking is much more sensitive to manipulations of the corticotrophin-releasing factor and noradrenaline systems than the DA system (Shaham et al. 2000). For instance, infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala prevents footshock-induced but not cocaine-induced reinstatement of cocaine seeking (Leri et al. 2002).

Rimonabant showed great promise as an antirelapse treatment; however, as mentioned above, it was removed from the European market as a treatment for obesity because of the undesirable side effects of anxiety. The generality of the effects of cannabinoids on motivational processes may explain these undesirable side effects. Given that rimonabant not only acts as a CB1 antagonist but is also a CB1 inverse agonist, the relapse-preventing properties, and potentially the adverse side effects, may also be mediated by its inverse cannabimimetic effects that are opposite in direction from those

produced by cannabinoid receptor agonists (Pertwee 2005). Recent evidence suggests that at least some adverse side effects of CB1 receptor antagonists/inverse agonists seen in clinical trials (e.g., nausea) may reflect their inverse agonist properties (Bergman et al. 2008). It will be of interest to evaluate the potential of more newly developed CB1 receptor neutral antagonists, such as AM4113 (Sink et al. 2008), to prevent drug-seeking behavior.

Recently, selective CB2 receptor agonists were shown to inhibit intravenous cocaine self-administration, cocaine-enhanced locomotion, and cocaine-enhanced accumbens extracellular dopamine in wild-type and CB1 receptor knockout mice but not in CB2 knockout mice. This effect was blocked by a selective CB2 receptor antagonist. These findings suggest that brain CB2 receptors also modulate cocaine's effects (Xi et al. 2011). Again, as mentioned above, the CB2 receptor seems to have general protective properties (Pacher & Mechoulam 2011).

Although considerable evidence indicates that antagonism of the CB1 receptor interferes with cue- and drug-induced relapse, there is a growing literature suggesting that FAAH inhibition and cannabidiol also prevent relapse to drug seeking. FAAH inhibition has been selectively evaluated for prevention of nicotine seeking (Forget et al. 2009, Scherma et al. 2008). However, it is not clear if these effects are mediated by the action of anandamide or other fatty acids [oleoylethanolamide (OEA) and palmitoylethanolamide (PEA)], which act on peroxisome proliferator-activated receptor- α (PPAR- α) receptors, because Mascia and colleagues (2011) recently showed that selective PPAR- α agonists also counteract the reinstatement of nicotine seeking in rats and monkeys. Thus, elevations in fatty acids produced by blockade of FAAH may have potential in treating relapse. Most recently, Cippitelli et al. (2011) found that FAAH inhibition reduced anxiety produced by nicotine withdrawal. Cannabidiol, the nonpsychoactive compound in marijuana, also attenuated cue-induced reinstatement of heroin seeking as well as restored disturbances of glutamatergic and endocannabinoid systems

in the accumbens produced by heroin seeking (Ren et al. 2009). Apparently, in addition to the many other ailments that cannabidiol improves (Mechoulam et al. 2002), it may also be a potential treatment for heroin craving and relapse.

CANNABINOIDS AND COGNITION

Cognition involves the ability to acquire, store, and later retrieve new information. Several recent reviews are available on the effects of cannabis on cognition in humans and other animals (Akirav 2011, Marsicano & Lafenetre 2009, Ranganathan & D'Souza 2006, Riedel & Davies 2005). Clearly, the chief psychoactive component in cannabis, THC, produces acute cognitive disturbances in humans and animals, more profoundly affecting short-term than long-term memory.

Effects of Cannabis on Cognition in Humans

When under the influence of THC, humans demonstrate transient impairment in short-term episodic and working memory and consolidation of these short-term memories into long-term memory, but no impairment in retrieval of information once it has been previously encoded into long-term storage (Ranganathan & D'Souza 2006). However, a recent naturalistic study revealed that cannabidiol prevented the memory-impairing effects of acute THC in humans (Morgan et al. 2010). Therefore, the relative THC/cannabidiol ratio in cannabis will profoundly modify the effects of cannabis on memory in human marijuana smokers.

The effect of chronic cannabis exposure on cognitive abilities of abstinent individuals is, however, controversial and fraught with contradictions in the literature. Polydrug abuse and pre-existing cognitive and emotional differences between cannabis users and nonusers make interpretation of the human literature problematical. In a review of the literature, Solowij & Battisti (2008) conclude that chronic exposure to marijuana is associated

with dose-related cognitive impairments, most consistently in attention and working memory functions—not dissimilar to those observed under acute intoxication. On the other hand, several reports indicate that few, if any, cognitive impairments are produced by heavy cannabis use over several years (e.g., Dregan & Gulliford 2012, Lyketso et al. 1999). More recently, a thorough review of the specific versus generalized effects of drugs of abuse on cognition (Fernandez-Serrano et al. 2011) reported that there has been only one study (Fried et al. 2005) of “pure” cannabis users. Fried et al. (2005) conducted a longitudinal examination of young adults using neurocognitive tests that had been administered prior to the first experience with marijuana smoke. Individuals were defined (by urination samples and self-reports) as light (fewer than five times a week) or heavy (greater than five times a week) current or former (abstinent for at least three months) users. Current heavy users performed worse than nonusers in overall IQ, processing speed, and immediate and delayed memory tests. In contrast, former heavy marijuana smokers did not show any cognitive impairment. Fernandez-Serrano et al. (2011) conclude that the acute effects of cannabis on prospective memory are attenuated in long-term abstinence (at least three months).

Drawing conclusions from the human literature is challenging (Ranganathan & D'Souza 2006) because of widely differing methodologies, including different tasks, lack of sufficient controls, participant selection strategies (only experienced cannabis users included in samples), different routes of administration, different doses administered, often small sample sizes, tolerance of and dependence on cannabinoids, and the timing of the test (given the long half-life of THC). In addition, factors such as a predisposition to substance use in general may confer greater vulnerability to cannabis-related cognitive effects. Therefore, experimental investigation of the effects of cannabinoids on various processes involved in learning and memory rely heavily upon animal models. These models provide insights into the critical role of the

endocannabinoid system in the physiology of learning and memory.

Effects of CB1 Agonists on Learning and Memory in Nonhumans

Consistent with the human literature, most reports using animal models suggest that acute administration of CB1 agonists selectively disrupts aspects of short-term or working memory while leaving retrieval of previously learned memory (long-term or reference memory) largely intact. A common behavioral paradigm designed to evaluate these different aspects of memory is the delayed matching (or nonmatching) to sample (DMS) task. Once the animal has learned to perform this operant task (reference memory), it must then indicate (usually by pressing a bar) which test sample matches (or does not match) the original sample stimulus presented several seconds earlier (working memory). CB1 agonists (THC and WIN-55,212) disrupt accuracy of such performance in a delay-dependent manner, consistent with a selective disruption of working memory (Heyser et al. 1993). These effects are blocked by the CB₁ antagonist rimonabant. It is important to note that these effects occur at doses that do not interfere with the acquisition of the original reference memory of the task. A simpler variant of the DMS procedure used in rodents, the spontaneous object recognition task, does not rely upon prior operant training, but instead relies upon a rodent's natural preference to explore novel objects. In this task, a rat or mouse is allowed to spontaneously explore two identical objects, then after a delay is given a choice to explore a novel object or the previously presented sample object. In this measure of short-term memory, CB1 agonists (WIN-55,212 and CP55,940) produced a delay-dependent deficit in discrimination between the novel and familiar objects in the choice task (O'Shea et al. 2004, Schneider & Koch 2002), with the disruptive effect enhanced 21 days after chronic pretreatment in adolescents but not adults (O'Shea et al. 2004).

Spatial memory tasks also rely upon accurate working memory. A demanding spatial

memory task is the 8-arm radial maze, which requires rats to first learn which arms contain food rewards (reference memory) and then to remember which arms have already been visited in a test session (working memory) after an imposed delay. THC increases the number of working memory errors (re-entries) at low doses, and these effects are blocked by rimonabant (Lichtman & Martin 1996). The impairment of working memory by THC (5 mg/kg) in adult rats is enhanced following chronic exposure (once a day for 90 days), but disappears following 30 days of abstinence from the drug (Nakamura et al. 1991). On the other hand, adolescent rats treated with very high escalating doses of THC (2.5–10 mg/kg) chronically for 10 days and left undisturbed for 30 days until their adulthood exhibited greater impairment in spatial working memory on the radial arm maze than did vehicle controls. The working memory deficit was also accompanied by a decrease in hippocampal dendritic spine density and length (Rubino et al. 2009).

The commonly employed spatial memory task, the Morris water maze, requires animals to navigate in a pool of water to locate a hidden platform by learning its location relative to salient visual cues. The water maze task can be used to evaluate the effect of cannabinoid agonists on reference memory (location of the platform remaining fixed across days and on trials within a day) and working memory (location of platform is changed each day, but remains constant across trials within a day). In the water maze task, THC disrupts working memory at much lower doses than those that disrupt reference memory; in fact, doses sufficient to disrupt working memory are below those that produce other effects characteristic of CB1 agonism, including antinociception, hypothermia, catalepsy, or hypomotility (Varvel et al. 2001). Vaporized marijuana smoke produces a similar effect (Niyuhire et al. 2007a).

Although exogenous CB1 agonists consistently suppress working memory in these models, manipulations that elevate endogenous cannabinoids do not consistently produce such an impairment. On the one hand, elevation

of anandamide (by FAAH inhibition), but not 2-AG (by MGL inhibition), interfered with the consolidation of contextual conditioned fear and object recognition memory (Busquets-Garcia et al. 2001); on the other hand, several other studies have reported facilitation of working memory by FAAH inhibition (Campolongo et al. 2009a, Mazzola et al. 2009, Varvel et al. 2007). Likewise, FAAH-deficient mice (with tenfold increases in brain levels of anandamide) also showed improved rather than impaired performance in this task. Therefore, the effects of exogenously administered CB1 agonists are not always consistent with the effects of manipulations that elevate the natural ligands for the receptors. However, FAAH inhibition also elevates several other fatty acids, including OEA and PEA, which are ligands for PPAR- α . Mazzola et al. (2009) recently found that the enhanced acquisition of a passive avoidance task by the FAAH inhibitor, URB597, was not only reversed by a CB1 antagonist, but also by a PPAR- α antagonist (MK 886). The PPAR- α agonist (WAY1463) also enhanced passive avoidance performance, and this effect was blocked by a PPAR- α antagonist (Campolongo et al. 2009a). Therefore, FAAH inhibition may enhance memory not only by increasing anandamide, but also by elevating OEA and PEA. Most recently, Pan et al. (2011) reported that MGL knockout mice, with elevated levels of 2-AG, show improved learning in an object recognition and water maze task. Thus, there is evidence that both anandamide and 2-AG enhance learning and memory under some conditions.

Effects of CB1 Antagonists on Learning and Memory in Nonhumans

The findings that CB1 agonists produce working memory deficits suggest that inhibition of these receptors may lead to enhancement of short-term memory. However, the literature is replete with mixed findings. CB1 antagonist administration produces memory enhancement in mice in an olfactory recognition task (Terranova et al. 1996) and a spatial memory task in an 8-arm radial maze (Lichtman 2000).

In addition, CB1^{-/-} mice are able to retain memory in an object recognition test for at least 48 hours after the first trial, whereas wild-type controls lose their capacity to retain memory after 24 hours (Reibaud et al. 1999). In contrast, studies using other paradigms, such as the DMS, have shown no benefits of rimonabant on learning or memory (e.g., Hampson & Deadwyler 2000, Mallet & Beninger 1998b). One explanation (Varvel et al. 2009) for the mixed findings is that the temporal requirements of the task predict the potential of CB1 antagonism to facilitate or not facilitate performance. Studies showing enhancement of memory generally require memory processes lasting minutes or hours, whereas studies showing that rimonabant is ineffective generally require retention of information lasting for only seconds, suggesting that blockade of CB1 receptors may prolong the duration of a memory rather than facilitate learning. If this is the case, then rimonabant may facilitate retention of memories tested after long intervals but may have no benefits in tasks such as DMS and repeated acquisition that require rapid relearning of new information (for review, see Varvel et al. 2009).

Role of Endocannabinoids in the Hippocampus in Learning and Memory

The decrement in working memory by cannabinoids appears to involve their action at the hippocampus. The hippocampus is one of the areas of the brain with the highest density of CB1 receptors, and large amounts of anandamide are found in the rodent hippocampus. Interestingly, the selective detrimental effect of CB1 agonists on working memory (but not reference memory) resembles the effects of hippocampal lesions on these two forms of memory (Hampson & Deadwyler 2000, Heyser et al. 1993). Furthermore, THC-induced deficits in the DMS paradigm are associated with specific decreases in firing of individual hippocampal neurons during the sample but not the match part of the experiment (Heyser et al. 1993). Intracranial administration of the CB1 agonists

directly into the hippocampus also disrupts working memory performance in an 8-arm radial maze (Lichtman et al. 1995, Wegener et al. 2008), water maze spatial learning (Abush & Akirav 2010), and object recognition memory (Clarke et al. 2008). In contrast, intrahippocampal AM251 also has been shown to disrupt memory consolidation of an inhibitory avoidance task (de Oliveira et al. 2005). Recent work suggests that the cannabinoid and the cholinergic systems in the hippocampus interact during performance of a short-term memory task in the rat (Goonawardena et al. 2010). These effects may be mediated by cannabinoid-induced decreases in acetylcholine release in the hippocampus. Acetylcholine is also implicated in the pathophysiology of Alzheimer's disease and other disorders associated with declined cognitive function.

Overall, the literature implicates changes in hippocampal functioning as the source of working memory deficits produced by THC, although other brain regions are currently being investigated as well (Marsicano & Lafenetre 2009). Cannabinoid receptors localized to different brain regions modulate distinct learning and memory processes, such that the role of endocannabinoids in other regions may be different than their role in the hippocampus. In fact, Campolongo et al. (2009b) showed that infusion of CB1 agonist WIN 55,212,2 into the basolateral amygdala actually enhanced consolidation of inhibitory avoidance learning by enhancing the action of glucocorticoids in this region. Consistently, Tan et al. (2011) found that delivery of a CB1 antagonist to this region interferes with olfactory fear conditioning. The differential effects of CB1 agonists on different brain regions may account for different findings reported between systemic and localized administration of cannabinoid agonists.

Long-term changes in synaptic strength are believed to underlie associative memory formation in the hippocampus and amygdala. The impairments in working memory produced by CB1 agonists may be the result of the suppression of glutamate release in the hippocampus, which is responsible for the establishment of

long-term potentiation, a putative mechanism for synaptic plasticity (Abush & Akirav 2010, Shen et al. 1996). Retrograde signaling by endocannabinoids results in suppression of neurotransmitter release at both excitatory (glutamatergic) and inhibitory (GABAergic) synapses in the hippocampus in a short- and a long-term manner. Endocannabinoid-induced long-term depression (LTD) is one of the best examples of presynaptic forms of long-term plasticity. Recent evidence indicates that presynaptic activity coincident with CB1 receptor activation and NMDA receptor activation is required for some forms of endocannabinoid LTD. The long-lasting effects of LTD appear to be mediated by a CB1 receptor-induced reduction of cAMP/PKA activity in the hippocampus (Heifets & Castillo 2009).

Endocannabinoid Modulation of Extinction of Aversive Memory

Avoidance of aversive stimuli is crucial for survival of all animals and is highly resistant to extinction. Considerable evidence indicates that the endogenous cannabinoid system is specifically involved in extinction learning of aversively motivated learned behaviors (Marsicano et al. 2002, Varvel & Lichtman 2002). A seminal paper by Marsicano et al. (2002) reported that CB1 knockout mice and wild-type mice administered the CB1 antagonist rimonabant showed impaired extinction in classical auditory fear-conditioning tests, with unaffected memory acquisition and consolidation. This effect appeared to be mediated by blockade of elevated anandamide in the basolateral amygdala during extinction (Marsicano et al. 2002). Using the Morris water maze task, Varvel & Lichtman (2002) reported that CB1 knockout mice and wild-type mice exhibited identical acquisition rates in learning to swim to a fixed platform; however, the CB1-deficient mice demonstrated impaired extinction of the originally learned task when the location of the hidden platform was moved to the opposite side of the tank. Because animals deficient in CB1 receptor activity show impairments

in suppressing previously learned behaviors, CB1 agonists would be expected to facilitate extinction of learned behaviors in nondeficient animals. Indeed, WIN-55,212 facilitated extinction of contextual fear memory and spatial memory in rats (Pamplona et al. 2006).

The effect of enhancing the endogenous levels of anandamide by blocking its reuptake or by inhibiting FAAH during extinction learning has also recently been investigated. Chhatwal et al. (2005) reported that the reuptake blocker (and FAAH inhibitor) AM404 selectively facilitated extinction of fear-potentiated startle in rats, an effect that was reversed by rimonabant pretreatment. Varvel et al. (2007) reported that mice deficient in FAAH, either by genetic deletion (FAAH^{-/-}) or by pharmacological inhibition, displayed both faster acquisition and extinction of spatial memory tested in the Morris water maze; rimonabant reversed the effect of FAAH inhibition during both task phases. These effects appear to be specific to extinction of aversively motivated behavior, because neither CB1-deficient mice (Holter et al. 2005) nor wild-type mice treated with rimonabant (Niyuhire et al. 2007b) displayed a deficit in extinction of operant responding reinforced with food. Most recently, Manwell et al. (2009) found that the FAAH inhibitor URB597 promoted extinction of a conditioned place aversion produced by naloxone-precipitated morphine withdrawal but did not promote extinction of a morphine-induced or amphetamine-induced CPP.

It has been well established that extinction is not unlearning, but instead is new inhibitory learning that interferes with the originally learned response (Bouton 2002). The new learning responsible for extinction of aversive learning appears to be facilitated by activation of the endocannabinoid system and prevented by inhibition of the endocannabinoid system. More recent work has suggested that the apparent effects of manipulation of the endocannabinoids on extinction may actually reflect its effects on reconsolidation of the memory that requires reactivation (Lin et al. 2006, Suzuki et al. 2008). That is, every time a consol-

idated memory is recalled it switches to a labile state and is subject to being disrupted. Depending upon the conditions of retrieval and the strength of the original trace, these reactivated memories can undergo two opposing processes: reconsolidation, when the conditions favor the permanence of the trace, or extinction, when the conditions indicate that the memory has no reason to persist. Suzuki et al. (2008) have proposed that the endocannabinoid system is important for the destabilization of reactivated contextual fear memories; that is, reconsolidation or extinction relies on a molecular cascade (protein synthesis and cAMP response element-binding-dependent transcription) that is impeded by prior blockade of the CB1 receptors. Fear memory cannot be altered during restabilization if it was not previously destabilized via activation of the CB1 receptor. Whatever the actual mechanism for facilitated extinction of aversive memories with activation of the endocannabinoid system and inhibited extinction with inhibition of the endocannabinoid system, these results have considerable implications for the treatment of posttraumatic stress disorder. Progress in enhancing endocannabinoid signaling will be of great benefit in the treatment of this distressing disorder.

CONCLUSIONS

Cannabinoid research was originally initiated with the limited aim of understanding the action of an illicit drug. After the chemistry of the plant and the pharmacological and psychological actions of THC were elucidated—or actually only assumed to be elucidated—in the 1960s and early 1970s, research in the field waned. However, over a decade starting from the mid-1980s, two specific receptors and their ligands—the bases of the endocannabinoid system—were found to be involved in a wide spectrum of biological processes. This endocannabinoid system has opened new vistas in the life sciences, particularly in aspects associated with the CNS.

One of the main results of activation of the presynaptic CB1 receptor is inhibition of neurotransmitter release. By this mechanism the

endocannabinoids reduce excitability of presynaptic neurons. CB1 receptors are responsible for the well-known marijuana effects as well as for effects on cognition, reward, and anxiety. In contrast, a major consequence of CB2 receptor activation is immunosuppression, which limits inflammation and associated tissue injury. Enhancement of CB2 receptor expression and/or of endocannabinoid levels has been noted in numerous diseases, including CNS-related ones. Thus, a main result of CB2 receptor activation seems to be a protective effect in a large number of physiological systems.

In the present review we have summarized evidence that cannabinoids modulate anxiety, brain reward function, and cognition by acting at CB1 (and possibly CB2) receptors in distinct brain regions. The effects of cannabis on anxiety appear to relate to the dose of THC and are modulated by the anxiolytic action of cannabidiol (if present in the plant material). A major function of the endocannabinoid system is the homeostatic regulation of the HPA axis in response to stressors. Although THC does not appear to be as rewarding as other drugs of abuse (cocaine, heroin, amphetamine) in animal models of drug abuse, recent work suggests that under optimal conditions, animals do self-administer THC. The rewarding effects of THC are mediated by elevation of DA in the mesolimbic DA system. Blockade of CB1 receptors in this system interferes with the potential of drugs or drug-related cues (but not stress) to produce relapse in animal models.

Both the animal and human literatures suggest that CB1 agonists interfere with short-term working memory and may interfere with consolidation of these memories into long-term memories while leaving previously learned long-term reference memory intact. In cannabis, these effects of THC may be prevented by a sufficiently high dose of cannabidiol. In addition, the memory-impairing effects of THC are usually limited to the acute effects of the drug itself. Recent literature suggests that the endocannabinoid system may play an especially important role in the extinction of aversively motivated learning. Treatments

that amplify the action of endocannabinoids may play a critical role in treating posttraumatic stress disorder in the future. Memory decline in aging may also be protected by the action of the endocannabinoid system. Mice lacking CB1 receptors showed accelerated age-dependent deficits in spatial learning as well as a loss of principal neurons in the hippocampus, which was accomplished by neuroinflammation (Albayram et al. 2011). These exciting findings suggest that CB1 receptors on hippocampal GABAergic neurons protect against age-dependent cognitive declines. In addition, interesting recent work suggests that cannabidiol reduces microglial activity after β -amyloid administration in mice and prevents the subsequent spatial learning impairment (Martin-Moreno et al. 2011), suggesting that this nonpsychoactive compound in marijuana may be useful in treating Alzheimer's disease. Cannabidiol has also been shown to recover memory loss in iron-deficient mice, a model of neurogenerative disorders (Fagherazzi et al. 2012).

A very large number of anandamide-like compounds, namely FAAAs or chemically related entities, have been found in the brain (Tan et al. 2010). The action of very few of them has been evaluated. However, those that have been investigated show a variety of effects. Arachidonoyl serine has vasodilator activity—an important protective property in some brain diseases—and lowers the damage caused by head injury (Cohen-Yeshurun et al. 2011). Surprisingly, this effect is blocked by CB2 antagonists, although this compound does not bind to the CB2 receptor. Apparently, its action is indirectly CB2 related. Oleoyl serine, which is antiosteoporotic, is also found in the brain (Smoum et al. 2010); oleoylethanolamide regulates feeding and body weight (Fu et al. 2005); stearoylethanolamide shows apoptotic activity (Maccarrone et al. 2002); the anti-inflammatory palmitoylethanolamide may also be protective in human stroke (Naccarato et al. 2010); arachidonoyl glycine is antinociceptive (Bradshaw et al. 2009); and arachidonoyl dopamine affects synaptic transmission in dopaminergic neurons

by activating both cannabinoid and vanilloid receptors (Marinelli et al. 2007). Presumably, the additional many dozens of related endogenous molecules found in the brain will also exhibit a wide spectrum of activities. Why does the brain invest so much synthetic endeavor (and energy) to prepare such a large cluster of related molecules rather than just a few of them?

If subtle chemical disparity is one of the causes for the variability in personality—an area in psychology that is yet to be fully understood—we may have to look for a large catalog of compounds in the brain with distinct CNS effects. Is it possible that the

above-described large cluster of chemically related anandamide-type compounds in the brain is related to the chemistry of the human personality and the individual temperamental differences? It is tempting to assume that the huge possible variability of the levels and ratios of substances in such a cluster of compounds may allow an infinite number of individual differences, the raw substance which of course is sculpted by experience. The known variants of CB1 and FAAH genes (Filbey et al. 2010, Lazary et al. 2010) may also play a role in these differences. If this intellectual speculation is shown to have some factual basis, it may lead to major advances in molecular psychology.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors would like to thank Erin Rock for editorial help. The authors were supported by a grant from the National Institute of Drug Abuse (U.S.) to R.M. (DA-9789) and from the Natural Sciences and Engineering Research Council of Canada (92057) to L.A.P.

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Contents

Prefatory

Shifting Gears: Seeking New Approaches for Mind/Brain Mechanisms
Michael S. Gazzaniga 1

Biological Bases of Behavior

The Endocannabinoid System and the Brain
Raphael Mechoulam and Linda A. Parker 21

Vision

Synesthesia
Jamie Ward 49

Scene Perception, Event Perception, Object Recognition

Visual Aesthetics and Human Preference
Stephen E. Palmer, Karen B. Schloss, and Jonathan Sammartino 77

Attention and Performance

Detecting Consciousness: A Unique Role for Neuroimaging
Adrian M. Owen 109

Executive Functions
Adele Diamond 135

Animal Learning and Behavior

The Neuroscience of Learning: Beyond the Hebbian Synapse
C.R. Gallistel and Louis D. Matzel 169

Evolutionary Psychology

Evolutionary Psychology: New Perspectives on Cognition
and Motivation
Leda Cosmides and John Tooby 201

Origins of Human Cooperation and Morality
Michael Tomasello and Amrisha Vaish 231

Language and Communication

- Gesture's Role in Speaking, Learning, and Creating Language
Susan Goldin-Meadow and Martha Wagner Alibali 257

Nonverbal and Verbal Communication

- The Antecedents and Consequences of Human Behavioral Mimicry
Tanya L. Chartrand and Jessica L. Lakin 285

Intergroup Relations, Stigma, Stereotyping, Prejudice, Discrimination

- Sexual Prejudice
Gregory M. Herek and Kevin A. McLemore 309

Social Neuroscience

- A Cultural Neuroscience Approach to the Biosocial Nature
of the Human Brain
*Shibui Han, Georg Northoff, Kai Vogeley, Bruce E. Wexler,
Shinobu Kitayama, and Michael E.W. Varnum* 335

Organizational Climate/Culture

- Organizational Climate and Culture
Benjamin Schneider, Mark G. Ehrhart, and William H. Macey 361

Industrial Psychology/Human Resource Management

- Employee Recruitment
James A. Breaugh 389

Learning and Performance in Educational Settings

- Self-Regulated Learning: Beliefs, Techniques, and Illusions
Robert A. Bjork, John Dunlosky, and Nate Kornell 417

Teaching of Subject Matter

- Student Learning: What Has Instruction Got to Do With It?
Hee Seung Lee and John R. Anderson 445

Health Psychology

- Bringing the Laboratory and Clinic to the Community: Mobile
Technologies for Health Promotion and Disease Prevention
Robert M. Kaplan and Arthur A. Stone 471

Research Methodology

- Multivariate Statistical Analyses for Neuroimaging Data
Anthony R. McIntosh and Bratislav Mišić 499

Social Network Analysis: Foundations and Frontiers on Advantage <i>Ronald S. Burt, Martin Kilduff, and Stefano Tasselli</i>	527
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Indexes

Cumulative Index of Contributing Authors, Volumes 54–64	549
Cumulative Index of Chapter Titles, Volumes 54–64	554

Errata

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Anxiogenic-like effects of chronic cannabidiol administration in rats

Maha M. ElBatsh · N. Assareh · C. A. Marsden ·
D. A. Kendall

Received: 13 June 2011 / Accepted: 28 October 2011 / Published online: 15 November 2011
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Abstract

Rational Several pre-clinical and human-based studies have shown that acutely administered cannabidiol (CBD) can produce anxiolytic-like effects

Objectives The present study investigated the effects of chronic administration of CBD on rat behaviour and on the expression of brain proteins.

Methods Male Lister-hooded rats (150–200 g, $n=8$ per group) received daily injections of CBD (10 mg/kg, i.p.) for 14 days. The rats were subjected to two behavioural tests: locomotor activity and conditioned emotional response (CER). The expression of brain-derived neurotrophic factor (BDNF), its receptor tyrosine kinase B (Trk B), extracellular signal-regulated kinases (ERK1/2) and phospho-ERK1/2 and the transcription factor cyclic AMP response element binding protein activation (CREB) and phospho-CREB were determined in brain regions such as the frontal cortex and hippocampus using Western immunoblotting.

Results CBD significantly increased the time spent freezing in the CER test with no effect on locomotor activity. CBD significantly reduced BDNF expression in the hippocampus and frontal cortex with no change in the striatum. In addition, CBD significantly reduced TrkB expression in the hippocampus with a strong trend

towards reduction in the striatum but had no effect in the frontal cortex. In the hippocampus, CBD had no effect on ERK1/2 or phospho-ERK2, but in the frontal cortex, CBD significantly reduced phospho-ERK1/2 expression without affecting total ERK.

Conclusion Chronic administration of CBD produced an anxiogenic-like effect in clear opposition to the acute anxiolytic profile previously reported. In addition, CBD decreased the expression of proteins that have been shown to be enhanced by chronic treatment with antidepressant/anxiolytic drugs.

Keywords Cannabidiol · Anxiety · BDNF · ERK · CREB · Hippocampus · Cannabinoids

Introduction

The *Cannabis sativa* plant contains at least 66 different cannabinoids, including the main psychoactive component, Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and other non-psychoactive components such as cannabidiol (CBD) (Ashton 2001; Mechoulam and Hanus 2002). Although the relative amounts of phytocannabinoids in cannabis preparations are highly variable, the content of CBD can exceed that of THC, in cannabis resin for example (Potter et al. 2008). CBD represents one of the most promising candidates for clinical utilisation, in a variety of conditions, due to its lack of cognitive and psychoactive actions and its excellent tolerability in humans (Mechoulam and Hanus 2002). Retrospective studies in cannabis users and small clinical trials have shown that moderate recreational or medicinal use of cannabis in humans results in mood elevation with a reduction in stress, anxiety and depressive symptoms (Gruber et al. 1996; Williamson and Evans

M. M. ElBatsh · N. Assareh · C. A. Marsden · D. A. Kendall
School of Biomedical Sciences,
University of Nottingham Medical School,
Queen's Medical Centre,
Nottingham NG7 2UH, UK

M. M. ElBatsh (✉)
Clinical Pharmacology Department, Faculty of Medicine,
Menofia University,
Shebin Elkom, Egypt
e-mail: maha.ali@med.menofia.edu.eg

2000), and some of these effects have been attributed to CBD. However, the molecular mechanisms underlying these effects are unclear, and several mechanisms of actions have been proposed for CBD, including diffuse targets within the endocannabinoid system (Bisogno et al. 2001), inhibition of serotonin reuptake and increased catecholaminergic activity (Russo and McPartland 2003), activation of serotonergic (5HT_{1A}) receptors (Russo et al. 2005), transient receptor potential type V1 (TRPV1) (Bisogno et al. 2001) and V2 (TRPV2) (Qin et al. 2008) and enhancement of adenosinergic signalling (Carrier et al. 2006). CBD, unlike Δ^9 -THC, has very low affinity for either cannabinoid CB1 or CB2 receptors (Petitet et al. 1998), but it has been shown to block the transport of anandamide, the archetypal endocannabinoid ligand (Bisogno et al. 2001) and to inhibit its enzymatic hydrolysis (Mechoulam and Hanus 2002). Thus, the action of CBD could involve other cannabinoid receptors such as the abnormal cannabidiol receptor, a non-CB1/non-CB2 receptor (Franklin and Stella 2003; Jarai et al. 1999). Actions of CBD at GPR55, an orphan G protein-coupled receptor, either as an agonist or antagonist have also been described (Oka et al. 2007; Ryberg et al. 2007).

Acute anxiolytic properties of CBD have been demonstrated in several preclinical studies that employed various paradigms such as the Vogel conflict test (Moreira et al. 2006), the elevated plus maze (Guimaraes et al. 1990) and fear conditioning (Lemos et al. 2010; Resstel et al. 2006). Recently, antidepressant-like effects have also been reported in mice following acute CBD administration (Zanelati et al. 2010). However, the effects of repeated CBD administration on affective behaviours in pre-clinical tests have not been reported.

The neurotrophin, brain-derived neurotrophic factor (BDNF), has been implicated in a variety of affective disorders including anxiety and depression (Bergami et al. 2009; Martinowich et al. 2007). Multiple classes of antidepressant drugs, as well as electroconvulsive shock treatment, can significantly increase BDNF messenger RNA (mRNA) expression in the hippocampus and prefrontal cortex (Duman and Monteggia 2006; Nibuya et al. 1995). This neurotrophin is thought to enhance neurogenesis (Li et al. 2008) via its receptor, tyrosine kinase B (TrkB), which activates a variety of downstream signalling pathways including extracellular signal-regulated kinases (ERKs) (Patapoutian and Reichardt 2001). Cyclic AMP response element binding protein activation (CREB) is one of the long-term transcriptional modulators that is thought to mediate the effects of antidepressants on BDNF expression (Malberg and Blendy 2005). The effects of repeated CBD administration on the expression and function of these signalling proteins are unknown.

Aim of the work

In order to assess the therapeutic potential of CBD for the treatment of affective disorders, it is necessary to understand the effects of repeated administration. Therefore, the aim of the present study was to test the hypothesis that repeated CBD administration would induce anxiolytic-like effects in aversive conditioned rats and modify the expression of proteins in the brain that have been associated with chronic antidepressant/anxiolytic drug treatments.

Material and methods

Animals

Male Lister-hooded rats (150–200 g, $n=16$) were obtained from the Biomedical Sciences Unit, University of Nottingham (a colony derived from Charles River UK stock). Animals were housed in groups of four and maintained on a 12/12-h light/dark cycle, temperature was maintained at $22\pm 2^\circ\text{C}$ and relative humidity 40–60%. Animals had free access to standard rat laboratory chow and water. All animal procedures were carried out in accordance with the UK Home Office Animals (Scientific Procedures) Act of 1986 and Local Ethical Committee Approval.

Drugs and treatment

Pure crystalline CBD (99.3% by HPLC with no other phytocannabinoids detectable) was a generous gift from GW Pharmaceuticals. It was dissolved in a vehicle of 3:1:16 solution of ethanol/Tween 80/0.9% saline. The rats received daily i.p. injections of either vehicle or CBD (10 mg/kg) for 14 days ($n=8$ per group). The dose of CBD was selected on the basis of other studies that reported effects of the drug in animal models of anxiety (Moreira et al. 2009; Moreira et al. 2006; Oviedo et al. 1993; Resstel et al. 2009; Resstel et al. 2006). Moreover, this dose of CBD (10 mg/kg) was reported to induce an anxiolytic-like effect after acute administration (Moreira et al. 2006; Resstel et al. 2006). CBD and vehicle solutions were prepared immediately before use and injected intraperitoneally (i.p.) in a volume of 1 ml/kg.

Procedures

Physiological measurements

Body weight and food consumption were measured daily throughout the experiment. Each cage housed four rats, and the average amounts of chow consumed per rat per day were determined.

Locomotor activity

Locomotor behaviour was recorded for 20 min on the third and ninth days of the experiment in a sound-isolated room (Fig. 1). The rats were habituated to the activity boxes (40×24×25 cm, clear acrylic) for 1 h on the second day. The activity boxes were cleaned with 20% (v/v) ethanol after removal of rats. Spontaneous locomotor activity, in terms of total distance moved (cm), mean velocity (cm/s) and rearing frequency, was recorded using Ethovision software [Ethovision (version 2.0), Noldus Information Technology, Costerweg, and The Netherlands]. The duration of periods of rearing and grooming was scored manually.

Conditioned emotional response testing

The conditioned emotional response (CER) has been used as a model of conditioned aversion in order to evaluate the anxiolytic effects of several classes of drugs such as selective serotonin reuptake inhibitors (Inoue et al. 1996) and benzodiazepines (Li et al. 2001). A conditioned fear response to a context is produced by exposing the animal to an environment (context) where an aversive or unpleasant stimulus (mild foot shock) is delivered (Rudy et al. 2004). Re-exposure to the same context induces conditioned fear responses, such as freezing behaviour.

The test consisted of two phases: conditioning on the 10th day and testing on the 11th day (Fig. 1). Rats were individually conditioned on the 10th day of the experiment by exposure to inescapable foot shock. Rats were subjected to 0.4 mA of footshock for 1 s every minute for 10 min in a shock chamber with a metal grid floor. This chamber had Perspex walls (26×23×39 cm) with 21 stainless steel rods spaced 1.5 cm apart as the floor, and this was and connected to a shock generator (Campden Instruments, Loughbrough, UK). Twenty-four hours after the last shock session, the rats were again placed in the shock chamber for 10 mins but without shocks, and freezing behaviour was measured. Freezing was defined as the complete absence of movement, except respiration, while the animal assumed a characteristic tense posture. The chamber was cleaned with 20% (v/v) ethanol before and after use (Finn et al. 2004a). The tests were all carried out between 0900 and 1300 hours.

Western immunoblotting

Rats were killed on day 15 of the experiment by a blow to the head followed by decapitation, and their brains were removed rapidly. The meninges were removed and brain regions dissected on ice and stored at −80°C. The expression of various proteins was measured in the hippocampus, frontal cortex and striatum.

Sample preparation A volume of lysis buffer [20 mM Tris, 1 mM EGTA, 320 mM sucrose, 0.1% Triton X100, 1 mM NaF and 10 mM beta-glycerophosphate dissolved in 500 ml distilled water (pH 7.6) containing protease inhibitor cocktail tablets (Sigma, UK)] was added based on the weights of frontal cortical samples to give a final concentration of 100 mg/ml. Samples were kept on ice through the assay all the time. The samples were homogenised by hand and mixed (rotating mixer) in a cold room for 10 min. The samples were centrifuged at 13,000×g for 10 min at 4°C. The supernatant was removed, and the Lowry test (Lowry et al. 1951) was performed to measure the protein concentrations in each sample. Laemmli solubilisation buffer (2×) was added to the samples to give a 1:2 dilution, then the protein concentration was adjusted using volumes of lysis buffer calculated from the protein assay. The samples were assayed immediately or stored at −20°C until needed. For CREB and phospho-CREB assays, the pellets were resuspended in lysis buffer to make a 3:5 dilution.

SDS gel electrophoresis Sodium dodecyl sulphate polyacrylamide electrophoresis gels (SDS-PAGE) were prepared in different concentrations suitable for running different proteins, e.g. 15% SDS-PAGE were used to run BDNF and TrkB immunoblots and 10% SDS-PAGE for CREB, phospho-CREB (p-CREB), ERK1/2 and phospho-ERK1/2 (p-ERK1/2). A layer of 4% gel (stacking gel) was added to the top of the running gel, and the comb was then placed into the gel to prepare ten wells.

Based on preliminary studies, 20–50 µg of protein was loaded onto each lane of the SDS gels. The gels were run in 1× running buffer [Tris (30.3 g), glycine (144 g) and SDS (10 g) dissolved in 1 L distilled water] at 200 V for 45 min using the Bio-Rad apparatus. A standard marker of known molecular weight (Bio-Rad laboratories Ltd, UK) was run alongside.

The proteins were transferred to nitrocellulose paper in the transfer buffer; Tris (30.3 g), glycine (144 g) and were dissolved in distilled water. Methanol (2 L) was added, then made up to 10 L with distilled water using the Bio-Rad apparatus at 100 V for 60 min at 4°C. Protein transfer was checked by adding a few drops of Ponceaus solution (Sigma, UK). The solution can be rapidly removed by washing with Milli-Q water then Tris-buffered saline-Tween (TBST) (25 mM Tris, 125 mM NaCl dissolved in distilled water, pH 7.6). The blots were blocked with 5% fat-free dried milk powder in TBST for 60 min using a platform shaker (Stuart Scientific, UK).

The specific primary antibodies for different proteins were prepared in 5% milk in TBST. The blots were kept in small plastic bags with the antibody overnight in the cold room (4°C) on a platform shaker (Stuart Scientific, UK).

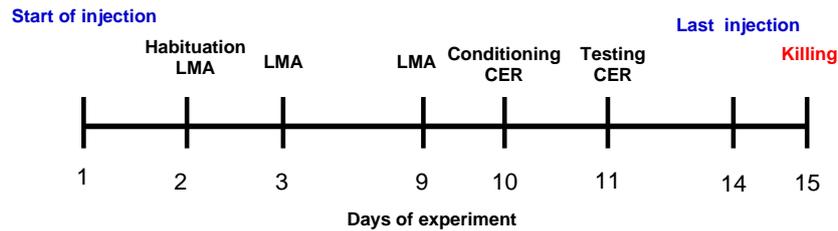


Fig. 1 Timeline showing the experimental protocol employed. Rats received daily intraperitoneal injection of vehicle or CBD (10 mg/kg). *LMA* Locomotor activity, *CER* conditioned emotional response. Note

Next day, the blots were washed three times with TBST buffer, then washed three times for 5 min and three times for 15 min.

The secondary antibody was prepared as 1:2,000 dilutions in 5% milk in TBST and added to the blots for 60 min at room temperature with shaking (Pardon et al. 2005).

In the dark room, the blots were exposed to enhanced chemiluminescence (ECL) reagent (Amersham Biosciences, UK) for 1 min then blotted dry on filter paper and wrapped in Saran wrap cling film. The blots were placed in an X-ray cassette and exposed to Hyperfilm ECL autoradiography film (Amersham Biosciences, UK) for 5–30 min. The films were developed using Kodak GBX developer (Sigma, UK), then fixed using Ilford Hypam rapid fixer (Ilford Imaging Ltd, UK). The developed films were scanned using a GS-710 Imaging Densitometer (Bio-Rad) and analysed using the Quantity One software package for image analysis

Antibodies Anti-BDNF (1:500, Santa Cruz Biotechnology, Inc.), anti-TrkB (1:1,000, upstate cell signalling), anti-CREB (1:1000, Cell Signalling Technology), anti-p-CREB (1:500, Cell Signalling Technology), anti-ERK1/2 (1:1,000, Cell Signalling Technology), anti-pERK (1:1,000, Cell Signalling Technology) and anti- β -actin (1:400,000, Sigma) primary antibodies were used. The secondary antibodies [horse-radish-peroxidase (HRP), DakoCytomation, Denmark] goat anti-rabbit IgG for BDNF, TrkB, ERK1/2, p-ERK1/2, CREB and p-CREB goat anti-mouse IgG for β -actin were prepared as 1:2,000 dilutions in 5% milk in TBST.

Statistical analysis

Data are presented as means \pm standard error of the mean (SEM). Data were analysed by Prism 4 software using unpaired *t* tests (for comparisons between treatment condition and the vehicle control) and the two-way repeated measures ANOVA for changes in body weight and food consumption over time followed by a Bonferroni post hoc test. Results were considered statistically significant if $P < 0.05$.

that the same groups of rats were used for all behavioural tests before killing for brain analysis on day 15

Results

Effect of repeated CBD administration on body weight

Body weight was measured daily between 0900 and 1000 hours. Two-way repeated measures ANOVA revealed significant increases in body weight with time [$F_{(14,196)} = 1041.0$; $P < 0.0001$], but there was no effect of treatment [$F_{(1,196)} = 0.02$; $P = 0.88$]. There were accompanying significant increases in food consumption with time [$F_{(13,26)} = 21.09$; $P < 0.0001$], but there was no effect of CBD treatment on the weight of food consumed [$F_{(1,26)} = 0.01$; $P = 0.93$] (data not shown).

Behavioural effects of repeated administration of CBD

Locomotor activity

The locomotor activity test was performed twice to detect any changes in locomotor activity over the course of CBD treatment. The first test was on the third day of drug injection, and the second was on the ninth day of treatment. CBD had no effect on total distance moved [$t_{(14)} = 1.4$; $P = 0.18$] or velocity [$t_{(14)} = 1.4$; $P = 0.18$] on the third day. This lack of effect of CBD on total distance [$t_{(14)} = 0.04$; $P = 0.97$] and velocity [$t_{(14)} = 0.04$; $P = 0.97$] continued to the ninth day.

Rearing and grooming behaviour were examined as markers of anxiety-related behaviour. CBD had no effect on rearing frequency [$t_{(10)} = 0.18$; $P = 0.86$], rearing duration [$t_{(13)} = 0.36$; $P = 0.72$] or grooming duration [$t_{(14)} = 0.30$; $P = 0.77$] on the third day or on the ninth day; on rearing frequency [$t_{(14)} = 0.11$; $P = 0.92$], rearing duration [$t_{(14)} = 0.38$; $P = 0.71$] or grooming duration [$t_{(14)} = 0.49$; $P = 0.63$].

Conditioned emotional response

The freezing behaviour of the rats was scored on the CER testing day (day 11). Freezing was expressed as a percentage of the total cage exposure time (10 min). Repeated administration of CBD significantly increased the time spent in freezing behaviour on the testing day of the CER procedure [$t_{(14)} = 2.76$; $P = 0.02$] (Fig. 2).

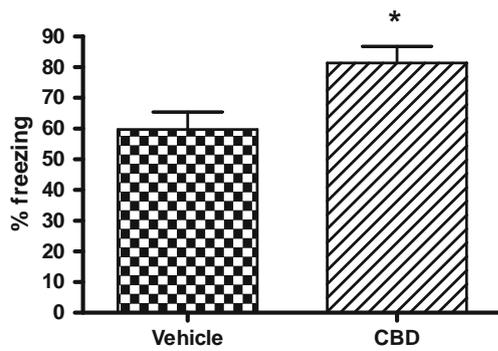


Fig. 2 Effects of chronic administration of CBD on percentage of time spent in freezing behaviour in the CER test on the test day (day 11 of the experiment). Columns represent the mean and bars represent the SEM. CBD significantly increased freezing compared to the vehicle-treated group; $n=8$ per group ($*P<0.05$)

Effect of chronic (14 days) CBD administration on protein expression

BDNF and TrkB

Western blots showed clear bands at the expected molecular weights for BDNF (13 kDa), TrkB (145 kDa) and β -actin (45 kDa) were used as a reference protein for equal loading (Fig. 3), and there were no differences in β -actin expression verifying equal gel loading of samples. The protein levels are presented as percentage changes compared with vehicle-treated control rats designated as 100%. CBD significantly reduced BDNF expression in the hippocampus [$t_{(14)}=3.31$; $P=0.005$] and frontal cortex [$t_{(14)}=2.47$; $P=0.027$], but there was no effect of CBD on BDNF expression in the striatum [$t_{(14)}=0.69$; $P=0.50$] (Fig. 4).

Moreover, CBD significantly reduced TrkB expression in the hippocampus [$t_{(14)}=3.36$; $P=0.005$] with a trend

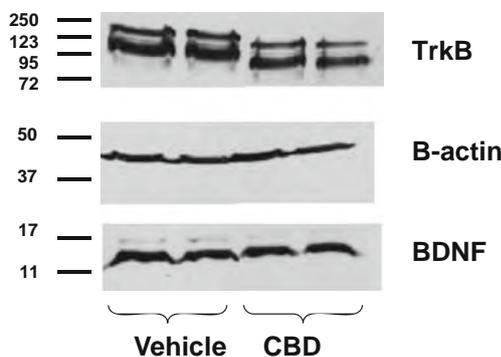


Fig. 3 Example of TrkB, β -actin and BDNF Western blots in the hippocampus. Western blots showed clear bands at the expected molecular weights for BDNF (13 kDa), TrkB (145 kDa) and β -actin (45 kDa). CBD reduced BDNF and Trk B expression in the hippocampus with equal loading

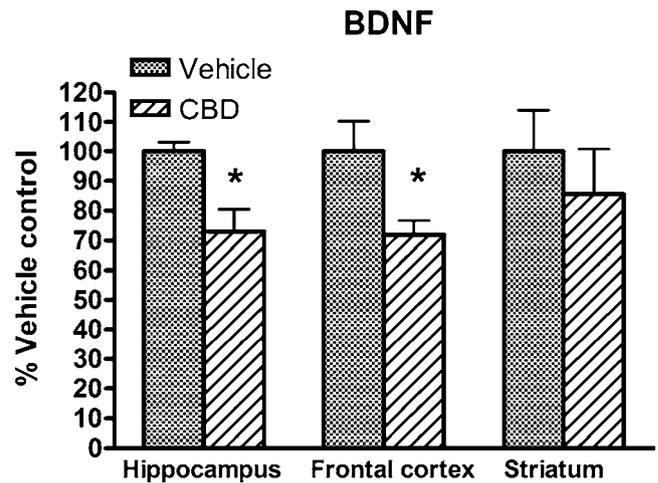


Fig. 4 Effect of chronic administration of CBD on BDNF expression. Data are expressed as percentage changes compared with the vehicle-treated group (designated as 100%) and presented as mean \pm SEM. Paired t tests were performed with Prism 4.0 software. $*P<0.05$ compared with vehicle, $n=8$ per group. CBD (10 mg/kg for 14 days) significantly reduced BDNF expression in the hippocampus and frontal cortex

towards a reduction expression in the striatum [$t_{(14)}=1.84$; $P=0.087$]. There was no effect of CBD on TrkB expression in the frontal cortex [$t_{(14)}=1.20$; $P=0.22$] (Fig. 5).

ERK1/2 and p-ERK 1/2 expression

Using Western immunoblotting, protein bands representing ERK 1/2 and p-ERK 1/2 were detected at 44 and 42 kDa in frontal cortex, although the p-ERK1

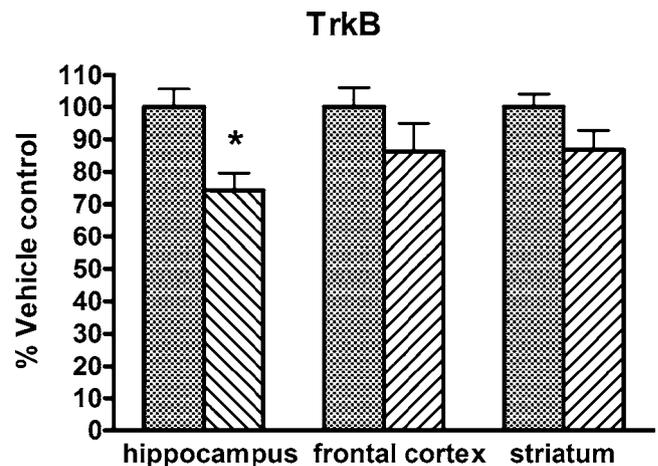


Fig. 5 Effect of chronic administration of CBD on TrkB expression. Data are expressed as percentage changes compared with the vehicle-treated group (designated as 100%) and presented as mean \pm SEM. Paired t tests were performed with Prism 4.0 software. $*P<0.05$ compared with vehicle, $n=8$ per group. CBD (10 mg/kg for 14 days) significantly reduced Trk B expression in the hippocampus

expression in the hippocampus was too low to detect. It should be noted that, although ERK1 and ERK2 were found at similar levels in the different brain areas, the signal was always much stronger for p-ERK2 than for p-ERK1, which was below the detection thresholds in some experiments (Fig. 6).

In the hippocampus, CBD had no effect on ERK1 [$t_{(14)}=0.89$; $P=0.39$], ERK2 [$t_{(14)}=0.67$; $P=0.51$] or p-ERK2 [$t_{(14)}=0.68$; $P=0.51$]. In the frontal cortex, CBD had no effect on ERK1 [$t_{(14)}=0.78$; $P=0.45$] or ERK2 [$t_{(14)}=0.77$; $P=0.45$] but significantly reduced p-ERK1 [$t_{(14)}=2.49$; $P=0.026$] and p-ERK2 [$t_{(14)}=2.46$; $P=0.028$] (Fig. 7).

CREB and p-CREB

Protein bands representing CREB and p-CREB were detected at 43 kDa in the frontal cortex, but p-CREB was undetectable in the hippocampus. CBD had no effect on CREB [$t_{(14)}=0.51$; $P=0.62$] or p-CREB [$t_{(14)}=0.33$; $P=0.75$] expression in the frontal cortex or CREB expression in the hippocampus [$t_{(14)}=1.20$; $P=0.25$].

Discussion

The phytocannabinoid CBD, which is one of the most abundant bioactive components of the cannabis plant, has been reported to have an acute anxiolytic effect in both animals and humans (Crippa et al. 2004; Lemos et al. 2010; Moreira et al. 2006; Zuardi et al. 1982). More recently, CBD has also been shown to have an acute antidepressant-like effect, via the activation of 5-HT_{1A} receptors, in a mouse forced-swimming test (Zanelati et al. 2010) without changing activity in the open field.

In the present study, no change in body weight was detected after administration of CBD for 14 days. On the contrary, Ignatowska-Jankowska et al. (2011) reported that repeated administration of CBD (2.5 and 5 mg kg⁻¹ day⁻¹)

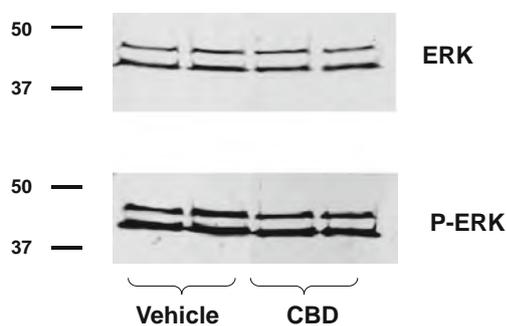


Fig. 6 Example Western blot of ERK and pERK expression in frontal cortex. Protein bands representing ERK 1/2 and p-ERK 1/2 were detected at 44 and 42 kDa in frontal cortex. CBD reduced both p-ERK1 and p-ERK2

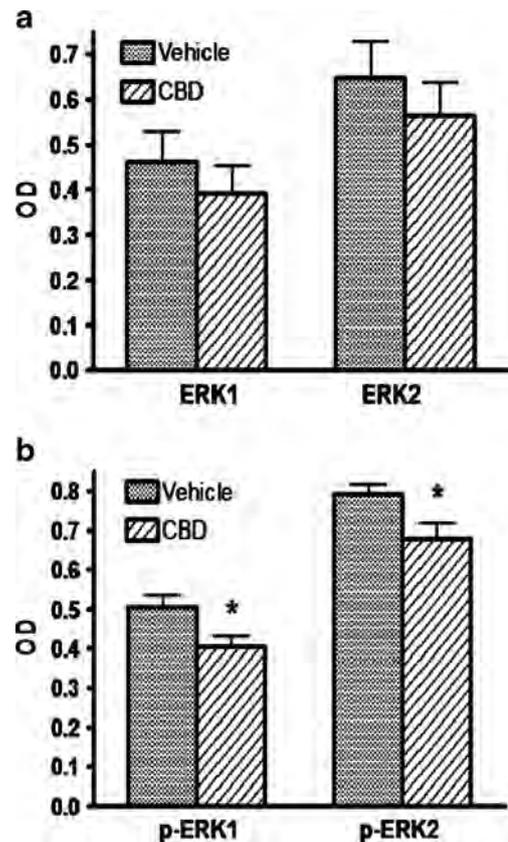


Fig. 7 Effect of chronic administration of CBD on protein expression of **a** ERK 1/2 and **b** p-ERK 1/2 in the frontal cortex. Unpaired *t* tests were performed with Prism 4.0 software. * $P<0.05$, $n=8$ per group. CBD (10 mg/kg for 14 days) significantly reduced p-ERK1/2 expression in the frontal cortex

for 14 days decreased the body weight gain of rats. This variance from the present study's findings may be related to the difference in species or dose of CBD used.

In the present study, the locomotor activity of the rats in a neutral environment was measured to detect any hypoactivity or changes in rearing and grooming hyperactivity associated with CBD treatment that could interfere with the interpretation of behavioural changes in the CER test. The administration of CBD (10 mg/kg, i.p. for 14 days) failed to affect the rats' spontaneous locomotor activity. This result is in agreement with Wiley et al. (2005) and Finn et al. (2004b) who reported that acute administration of CBD had no effect on locomotor activity of mice or rats respectively.

Rearing and grooming were examined as markers of anxiety-related behaviour as increased self-grooming in rats is frequently observed after the application of mild stressors, such as novelty or handling of the animals (van Erp et al. 1994). Anxiolytic drugs attenuate the increase in grooming induced by a novel environment without significantly affecting general locomotor activity,

which dissociates grooming activity from sedation (Dunn et al. 1981; Moody et al. 1988).

In the present study, there were no differences in rearing and grooming between the treatment groups in agreement with Finn et al. (2004b), who found that rearing and grooming were unaltered by acute administration of a lower dose of CBD (5 mg/kg).

In the CER test, however, the rats were exposed to an environment paired previously with inescapable electric foot shock, which results in a well-characterised freezing response. The duration of freezing has been used as an index of induced fear and anxiety (Fanselow 1980), and a number of anxiolytic drugs decrease the duration of freezing (Hashimoto et al. 1996; Inoue et al. 1996).

Resstel et al. (2006) observed that acute injection of CBD (10 mg/kg, i.p.) reduced the freezing time in conditioned rats, and Bitencourt et al. (2008) reported that CBD facilitated conditioned fear extinction in rats, which might contribute to the anti-anxiogenic effect detected in the same study. In the present study, it was hypothesised that CBD would induce an anxiolytic-like effect in the CER test in the form of reduced conditioned freezing. However, on the contrary, repeated CBD administration significantly *increased* the time spent in freezing behaviour indicating an anxiogenic-like effect after chronic administration.

There were some differences in methodology between the present study and those previously reporting anxiolytic effects. For example, rats were individually housed in the study of Resstel et al. (2006), while they were group housed in the present study. There were also differences the conditioning protocols in that the rats received six 2.5 mA foot shocks in the study of Resstel et al. (2006) and ten 0.4 mA shocks in the present study. Nevertheless, it seems unlikely that the qualitative differences in behavioural outcomes between acute and chronic administration of CBD could be explained by relatively minor variations in methodology. It is noteworthy that the anxiolytic effect of CBD in humans has only been reported after acute administration (Zuardi et al. 2006).

Long et al. (2009), however, demonstrated that chronic daily administration of CBD to male adult C57BL/6JArc mice for 21 days produced moderate anxiolytic-like effects in the open-field test at 50 mg/kg and in the light–dark test at a low dose (1 mg/kg). This variance from the present study's findings may be related to the species used, the behavioural test employed or the dose and duration of CBD administration. For example, in the study of Magen et al. (2009) the optimal dose of CBD for cognitive enhancement in the bile duct ligation model was 5 mg/kg over a 4-week period, while 1 and 10 mg/kg were ineffective. This indicates a complex dose–response relationship for CBD, at least in this model, which complicates interpretation of inter-study differences. Although the dose of CBD used in

the present study was reported to induce an anxiolytic-like effect after acute administration in previous studies (Moreira et al. 2006; Resstel et al. 2006), a biphasic effect of CBD was reported in other studies (Guimaraes et al. 1990; Kwiatkowska et al. 2004; Malfait et al. 2000; Rock et al. 2008), which emphasises the need for additional long-term multi-dose studies.

The neurotrophic hypothesis of depression (Nestler et al. 2002) suggests that BDNF is reduced in depression and increased by many antidepressant/anxiolytic treatments. We hypothesised that CBD might increase expression of BDNF protein, its receptor (TrkB) or the downstream mitogen-activated protein kinase (MAPK) signalling protein cascade (ERK). This is, of course, relevant to potential anxiolytic actions of CBD since antidepressant drugs are the first line therapy for long-term anxiety (Dell'Osso et al. 2010). We focused on the hippocampus, frontal cortex and striatum as these brain areas may be dysfunctional in affective disorder (Kennedy et al. 1997; Sheline 2000). However, in the present study, Western immunoblotting showed that chronic administration of CBD significantly *decreased* BDNF expression in the hippocampus and frontal cortex while having no effect on BDNF levels in the striatum. Moreover, CBD also significantly reduced TrkB expression in the hippocampus with a strong trend towards a decrease in the striatum but with no effect in the frontal cortex. Magen et al. (2009) reported that chronic administration of CBD (5 mg/kg) for 4 weeks to female Sabra mice had no effect on BDNF mRNA in the hippocampus but normalised the reduced BDNF after bile duct ligation, a model of hepatic encephalopathy. Zanelati et al. (2010) reported that acute administration of CBD (30 mg/kg) did not affect BDNF expression in the mouse hippocampus, although it showed an antidepressant-like effect in the forced swim test.

Previous studies have demonstrated that chronic antidepressant treatment increases the expression of CREB in limbic regions of rat brain (Nibuya et al. 1996). CREB in its phosphorylated form is a transcription factor that mediates the actions of intracellular messengers on gene expression. The function of CREB is regulated largely by phosphorylation at Ser¹³³, which results in activation of gene transcription (Thome et al. 2000). CREB activation could alter the expression of specific gene products involved in the modulation of anxiety, such as BDNF and could, thereby, underlie some of the effects of antidepressant treatment on long-term anxiety. Since the phosphorylation of CREB may be mediated by the MAPK pathway through the phosphorylation of ERK and TrkB signals, at least partly, through MAPK activation, we focused our attention on the effects of CBD on p-CREB and p-ERK induction.

In the present study, CBD had no effect on CREB expression in the frontal cortex and hippocampus or p-

CREB expression in the frontal cortex, while in the hippocampus, p-CREB was undetectable. With respect to ERK and p-ERK, CBD significantly reduced p-ERK1/2 in the frontal cortex without affecting total ERK1/2 expression, and there was no apparent change in ERK1/2 or p-ERK2 expression in the hippocampus.

Given the pleiotropic effects of cannabidiol, it is difficult to propose a straightforward molecular mechanism to explain the effects of the drug on the expression of these proteins, but, although no direct assessments of neurogenesis were made in these animals, the combined negative effects of cannabidiol on BDNF and BDNF-related signalling proteins would certainly not be consistent with the enhanced neurogenesis reported for clinically effective antidepressants/antxiolytics and would probably predict the opposite.

Conclusion

The data presented indicate an anxiogenic-like profile of behaviour in normal healthy rats following repeated CBD administration. This was accompanied by reductions in the expression of the neurotrophin BDNF and related signalling proteins, and, overall, the results are not consistent with the potential clinical anxiolytic properties suggested by acute experiments with CBD. This emphasises the need for additional long-term multi-dose studies of the drug in models of affective disease.

Acknowledgements We would like to thank GW Pharmaceuticals for kindly supplying the CBD.

Disclosure/conflict of interest The authors have no conflicts of interest to disclose

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Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow

José Alexandre de Souza Crippa^{*1,4}, Antonio Waldo Zuardi¹, Griselda EJ Garrido², Lauro Wichert-Ana¹, Ricardo Guarnieri¹, Lucas Ferrari³, Paulo M Azevedo-Marques³, Jaime Eduardo Cecílio Hallak¹, Philip K McGuire⁴ and Geraldo Filho Busatto⁵

¹Department of Neuropsychiatry and Medical Psychology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil; ²Division of Informatics, Heart Institute (InCor), Faculty of Medicine, University of São Paulo, Brazil; ³Department of Medical Clinic, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil; ⁴Department of Psychological Medicine, Section of Neuroimaging, Institute of Psychiatry, University of London, UK; ⁵Department of Psychiatry, Faculty of Medicine, University of São Paulo, Brazil

Animal and human studies have suggested that cannabidiol (CBD) may possess anxiolytic properties, but how these effects are mediated centrally is unknown. The aim of the present study was to investigate this using functional neuroimaging. Regional cerebral blood flow (rCBF) was measured at rest using ^{99m}Tc-ECD SPECT in 10 healthy male volunteers, randomly divided into two groups of five subjects. Each subject was studied on two occasions, 1 week apart. In the first session, subjects were given an oral dose of CBD (400 mg) or placebo, in a double-blind procedure. SPECT images were acquired 90 min after drug ingestion. The Visual Analogue Mood Scale was applied to assess subjective states. In the second session, the same procedure was performed using the drug that had not been administered in the previous session. Within-subject between-condition rCBF comparisons were performed using statistical parametric mapping (SPM). CBD significantly decreased subjective anxiety and increased mental sedation, while placebo did not induce significant changes. Assessment of brain regions where anxiolytic effects of CBD were predicted *a priori* revealed two voxel clusters of significantly decreased ECD uptake in the CBD relative to the placebo condition ($p < 0.001$, uncorrected for multiple comparisons). These included a medial temporal cluster encompassing the left amygdala–hippocampal complex, extending into the hypothalamus, and a second cluster in the left posterior cingulate gyrus. There was also a cluster of greater activity with CBD than placebo in the left parahippocampal gyrus ($p < 0.001$). These results suggest that CBD has anxiolytic properties, and that these effects are mediated by an action on limbic and paralimbic brain areas.

Neuropsychopharmacology (2004) 29, 417–426, advance online publication, 29 October 2003; doi:10.1038/sj.npp.1300340

Keywords: cannabidiol; anxiety; regional cerebral blood flow; SPECT; neuroimaging

INTRODUCTION

Cannabidiol (CBD) constitutes up to 40% of *Cannabis sativa* (Grille, 1976) and has quite different psychological effects to the plant's best known constituent, Δ^9 -tetrahydrocannabinol (Δ^9 -THC) (Perez-Reyes *et al*, 1973; Zuardi *et al*, 1982). In particular, in animal studies CBD has effects similar to anxiolytic drugs in conditioned emotional paradigms (Zuardi and Karniol, 1983), the Vogel conflict

test (Musty *et al*, 1984), and the elevated plus maze test (Guimaraes *et al*, 1990; Onaivi *et al*, 1990). Using the latter test, anxiolytic effects were also reported for three derivatives of CBD, HU-219, HU-252, and HU-291 (Guimaraes *et al*, 1994). In humans, oral administration of CBD in healthy volunteers attenuates the anxiogenic effect of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) (Zuardi *et al*, 1982). This effect does not seem to involve any pharmacokinetic interactions (Aguirell *et al*, 1981; Zuardi *et al*, 1982), and CBD does not bind to the central known cannabinoid receptor, CB₁, (Bisogno *et al*, 2001; Mechoulam *et al*, 2002) and hence cannot be a competitive antagonist (Howlett *et al*, 1992). CBD may thus possess inherent anxiolytic properties unrelated to THC-type activity. This is consistent with its anxiolytic effect on anxiety elicited by simulated public speaking (Zuardi *et al*, 1993a).

As the receptors that mediate the psychological effects of CBD are unknown, its mechanism of action on the brain is unclear. The aim of the present study was to use functional

*Correspondence: JAS Crippa, Departamento de Neuropsiquiatria e Psicologia Médica, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Hospital das Clínicas-Terceiro Andar, Av. Bandeirantes, 3900 Ribeirão Preto, São Paulo, CEP-14049-900, Brazil, Tel: + 55 16 6022703, Fax: + 55 16 6350713,

E-mail: jcrippa@directnet.com.br

Received 22 April 2003; revised 22 August 2003; accepted 25 September 2003

Online publication: 29 September 2003 at <http://www.acnp.org/citations/Npp09290303172/default.pdf>

neuroimaging to investigate this. In view of its anxiolytic effect, we tested the hypothesis that CBD would affect neural activity in areas that normally mediate anxiety. We compared the effects of CBD and placebo on resting cerebral regional blood flow (rCBF) in healthy volunteers in a double-blind, cross-over design. Based on previous functional imaging studies of anxiety (Maddock and Buonocore, 1997; Fischer *et al*, 1996; Liotti *et al*, 2000; Ketter *et al*, 1996), we predicted that, relative to placebo, CBD would modulate rCBF in limbic and paralimbic areas: the orbitofrontal, cingulate and medial temporal cortex, and the insula.

MATERIALS AND METHODS

Subjects

A total of 10 healthy male postgraduate students were studied. None had undergone rCBF SPECT examinations or other nuclear medicine procedures before. All were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and were nonsmokers (of tobacco). Their mean age was 29.8 years (range 25–42 years, SD = 5.1), their mean weight was 74.1 kg (67–85 kg, SD = 6.05), and their body mass index ranged between 21 and 25 kg/m². The subjects had not taken any medicines for at least 3 months before the study (Mathew *et al*, 1992). No subject had a history of head trauma, neurological, or major medical illnesses, based on a semistandardized medical questionnaire and physical examination. Neither the subjects (based on the Structured Clinical Interview for DSM-IV, First *et al*, 1997) nor their first-degree relatives (based on subjects' report) had a history of psychiatric illness. No subject had used marijuana more than five times in their lives (nor in the last year), and none had used any other illegal drug. The experiment was conducted with the understanding and consent of each subject, following approval by the local ethical committee.

Cannabidiol

CBD in powder, approximately 99.9% pure (supplied by THC-Pharm, Frankfurt, Germany), was dissolved in corn oil (Zuardi *et al*, 1993a, 1995). The same amount of corn oil was used as a placebo. The drug and placebo were packed inside identical gelatin capsules.

Self-Rating Scale

Subjective states were evaluated by means of the Visual Analogue Mood Scale (VAMS) of Norris (1971), translated into Portuguese by Zuardi and Karniol (1981b). It consists of 16 analogue scales to measure drug effects, which were arbitrarily divided by Norris into four factors: anxiety, physical sedation, mental sedation, and other feelings and attitudes. A factor analysis with the Portuguese version of this scale (Zuardi *et al*, 1993a) extracted four factors that can be identified with those of the Norris proposal. Prior to the experiment, each volunteer had performed a training session completing this scale.

Procedure

Subjects were told not to consume any alcohol for 24 h and caffeine for at least 4 h before each visit to the laboratory (Mathew *et al*, 1999). Subjects who reported having less than 6 h of sleep the previous night were excluded. After at least 8 h of fasting, subjects were instructed to have a light, standardized breakfast 2 h before the experiment. They were randomly divided into two groups of five subjects. Each subject was evaluated on two different occasions, 1 week apart. In the first session, after a 30-min period of adaptation, subjects were given a single dose of oral CBD (400 mg) or placebo, in a double-blind procedure. The sessions were held in the morning (between 0800 and 1200) to minimize the effects of circadian variation. SPECT image acquisition was performed 110 min after drug ingestion. Subjective ratings on the VAMS were made 30 min before drug ingestion, at the time of drug ingestion, and at 60 min and at 75 min afterwards. In the second session, an identical procedure was followed except that the other drug was administered (ie those given CBD in the first session received placebo in the second; and *vice versa*). Subjects were informed that they would receive CBD and placebo, but they were not told in which order. The investigators were also blind to the content of the capsules.

SPECT

Subjects had a venous cannula inserted into their right arm, and rested supine with minimal environmental sensory stimulation. They were instructed to keep their eyes closed under eye pads and to relax for 15 min without falling asleep. Their ears were unplugged. VAMS ratings were made just before and 15 min after insertion of the venous cannula. At 30 min after insertion of the venous cannula, 740 MBq (20 mCi) of ethyl-cisteinate-dimer (ECD) labeled with technetium-99m (^{99m}Tc-ECD) was injected. Subjects rested for an additional period of 5 min postinjection, after which the venous cannula was removed.

Image acquisition started 20 min after the ^{99m}Tc-ECD injection, using a double-detector SOPHA[®] DST system (Sophy Medical Vision, Twinsburg, USA). High-resolution low-energy collimators were used, with 128 views acquired on a 128 × 128 matrix (30 s per view), with a total acquisition time of 30 min, and approximately 75 000 counts/frame/head. Raw images were prefiltered with a Butterworth filter (order number 4, cutoff frequency 0.16), and reconstructed by filtered back-projection as transaxial slices parallel to the long axis of the temporal lobe. Attenuation correction was performed considering a pixel size of 2.55 mm and using the first-order algorithm of Chang (coefficient 0.12/cm).

Image Processing and Analysis

Images were analyzed using Statistical Parametric Mapping software (SPM99) (Friston *et al*, 1995). Reconstructed transaxial datasets were transferred to a PC (Pentium IV, 2.2 GHz, 512 Mb RAM), converted to Analyze format and reoriented to neurological convention (ie left = left).

Placebo images were realigned to CBD images using sinc interpolation. Linear (translations and rotations) and non-linear ($7 \times 8 \times 7$ nonlinear basis functions) deformations were used to register images to the SPM SPECT template, which is based on the Montreal Neurological Institute (MNI) template (Mazziotta et al, 1995). Finally, an isotropic Gaussian filter of 12 mm was applied to diminish inter-individual differences, and to conform data to the theory of Gaussian Random Fields (Friston et al, 1995), in order to allow the subsequent application of parametric statistical tests.

Between-condition (CBD vs placebo) comparisons of regional tracer uptake were performed on a voxel-by-voxel basis using paired *t*-tests. Before statistical testing, the regional ECD uptake of every voxel in each subject was standardized to the mean global uptake of the image in that subject, using proportional scaling. Only voxels with signal intensities above a threshold of 0.8 of the global mean (calculated using the standardized values) entered the statistical analysis. The resulting statistics at each voxel were transformed to *Z*-scores, thresholded at $Z=2.33$ (corresponding to $p<0.01$, one-tailed), and displayed as 3-D statistical parametric maps (SPM). These maps were first inspected for the presence of voxel clusters of significant difference in the regions where effects of CBD had been predicted *a priori* (medial temporal, cingulate, orbitofrontal, and insular cortices). Clusters in these regions were considered as significant if they included voxels with *Z*-scores of 3.09 or greater (corresponding to one-tailed $p<0.001$), and contained more than 20 voxels. Levels of $p<0.001$, uncorrected for multiple comparisons, have been frequently used in previous SPM analyses of positron emission tomography (PET) (Dougherty et al, 1999; Bremner et al, 1999b) and SPECT (Blackwood et al, 1999; Busatto et al, 2000) data, and are considered to provide good protection against false-

positive results when there are clear hypotheses as to the location of findings. The SPMs were also inspected for differences in other, unpredicted regions. These areas were reported as significant if they survived a correction for multiple comparisons based on Gaussian random field theory ($p<0.05$) (Friston et al, 1995).

For each voxel cluster showing significant between-condition differences, estimates were calculated for the mean, median, and maximal percentages of ECD count rate change (and their variances) (Table 1). These indices were obtained by partitioning the Student's *t*-test value of each voxel into its main components, with the numerator of the *t* statistic used as an approximation of the magnitude of the signal change for each contrast (placebo > CBD or CBD > placebo), and the denominator (the standard error) used to calculate the variances. The MNI coordinates for the voxels of maximal statistical significance for each anatomical brain region included in a given cluster were converted to the Talairach and Tournoux (1988) system using the method described by Brett et al (2002).

The four VAMS factors were submitted to an ANOVA for repeated measures in both CBD and placebo sessions. The differences between CBD and placebo in each phase of the experimental session (-30, 0, 1'00, 1'15) were analyzed by *t*-tests. Correlations between the regional tracer uptake and each of the VAMS factors scores were also investigated with SPM99, at the same statistical significance levels as described above for the between-condition rCBF comparisons. The last point in which the VAMS was applied (75' after drug intake) was chosen for these correlations due to its proximity to the injection of the SPECT tracer. Moreover, this is the point where CBD is expected to have its maximum anxiolytic effect among all the time points chosen for assessment during the experimental session (Zuardi et al, 1993a). The choice for

Table 1 Limbic and Paralimbic Areas of Significant rCBF Differences in CBD Compared to Placebo Condition

Finding and cluster ^a	Cluster mean ^b and median ^c % signal change	Cluster mean ^b and median ^c variance	P-value (corrected) ^d	Regions included in cluster	Peak ^e % signal change (variance)	Peak ^e Z-score ^f	Coordinates ^g		
							x	y	z
<i>Placebo > CBD</i>									
Cluster 1 (102 voxels)	4.61	9.51	0.99	Left posterior cingulate cortex (BA 31)/paracentral lobule (BA5/6)	4.81 (4.51)	3.40	-4	-27	47
	4.57	8.72							
Cluster 2 (203 voxels)	4.63	10.83	1.00	Left hypothalamus Left amygdala-hippocampal complex /uncus	5.61 (8.26)	3.12	-6	-6	-8
	4.56	10.53			3.77 (4.53)				
<i>CBD > Placebo</i>									
Cluster 3 (114 voxels)	5.06	10.88	0.96	Left parahippocampal / fusiform gyri	4.53 (2.91)	3.69	-30	-15	-24
	5.17	10.14							

^aTotal number of voxels in each cluster that surpassed the initial threshold of $Z=2.33$ are shown between parentheses.

^bAverage of all the voxel values in the cluster.

^cMiddle value in the distribution of frequencies of the cluster.

^dLevel of statistical significance after correction for multiple comparisons using Gaussian random field theory (Friston et al, 1995).

^eVoxel of maximal statistical significance in the cluster.

^fZ-score for the voxel of maximal statistical significance within each cluster.

^gTalairach and Tournoux (1988) coordinates obtained through the conversion of SPM MNI (Mazziotta et al, 1995) coordinates according to Brett et al (2002).

this time point was also based on previous studies, which have shown that the plasma peak of an oral dose of CBD usually occurs between 1 and 2 h after ingestion (Agurell et al, 1981).

RESULTS

Visual Analogue Mood Scale

The administration of CBD was associated with significantly decreased subjective anxiety ($F(3,27) = 18.56$, $p < 0.001$) and increased mental sedation ($F(3,27) = 42.85$, $p < 0.001$), while placebo was not ($F(3,27) = 1.86$, $p = 0.16$ and $F(3,27) = 2.24$, $p = 0.11$, respectively) (Figure 1). In addition, an analysis at each time point indicated the following: (i) CBD was associated with significantly decreased anxiety at cannula insertion (60' after drug intake, $t = 2.95$, $p = 0.009$) and resting phases (75' after drug intake, $t = 5.50$, $p < 0.001$) as compared to placebo; (ii) CBD was associated with significantly increased feelings of mental sedation at cannula insertion (60' after drug intake, $t = -3.91$, $p = 0.001$) and resting phases (75' after drug intake, $t = -3.67$, $p = 0.002$) as compared to placebo.

Between-Condition rCBF Comparisons

The SPM showing increases in ECD uptake in the CBD relative to placebo condition revealed only one cluster (> 20 voxels) that surpassed the initial $Z = 2.33$ statistical cutoff (Figure 2). This cluster, which achieved statistical significance at the $p < 0.001$ level (uncorrected for multiple comparisons), was located in the medial temporal cortex, where the effects of CBD had been predicted *a priori*, and involved the left parahippocampal gyrus,

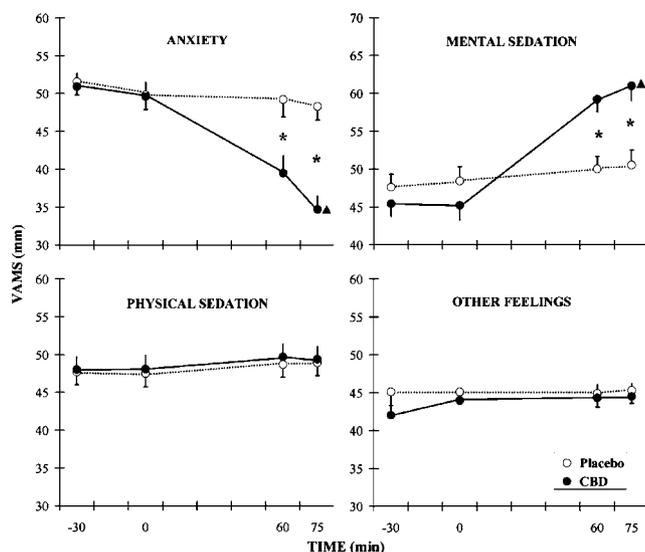


Figure 1 Effect of CBD and placebo (PLCB) on the four factors of the VAMS. Points are means (\pm SEM) of 10 healthy subjects in the following phases of the experiment: predrug (-30), drug intake (0), prestress (60), and adaptation (75). Asterisk (*) indicates significant difference from placebo in each phase. Triangle (\blacktriangle) indicates ANOVA significant changes.

extending inferiorly to encompass the left fusiform gyrus (Table 1).

Significantly decreased ($p < 0.001$, uncorrected for multiple comparisons), ECD uptake in the CBD relative to the placebo condition was evident in two regions where effects of CBD had been predicted *a priori* (Table 1). One cluster included the medial portion of the left amygdala-hippocampal complex and uncus, as well as the hypothalamus. The other was located in the superior portion of the left posterior cingulate gyrus (Brodmann area—BA31),

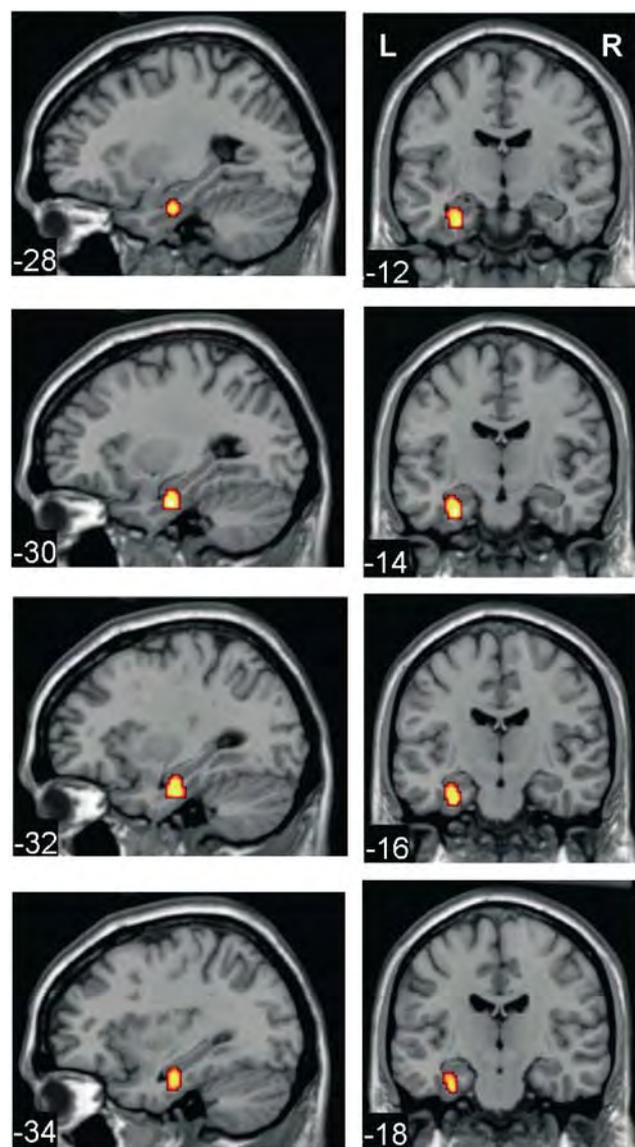


Figure 2 The brain region where there was significantly increased rCBF in healthy volunteers ($n = 10$) during CBD vs placebo has been overlaid on coronal sections (-18, -16, -14, -12) and sagittal sections (-28, -30, -32, -34) of a reference brain, imaged with structural MRI and spatially normalized into an approximation to the Talairach and Tournoux (1988) stereotactic atlas. The results are displayed in neurological convention (ie left = left). The numbers associated with each frame represent the standard coordinate in the y - (for the coronal frames) and x -axis (for the sagittal frames). The voxel cluster shown was located in the left parahippocampal gyrus extending inferiorly to encompass the left fusiform gyrus (peak Z -score = 3.69, coordinates $_{xyz} = -30, -14, -30$; $p < 0.0001$ uncorrected for multiple comparisons; 114 voxels).

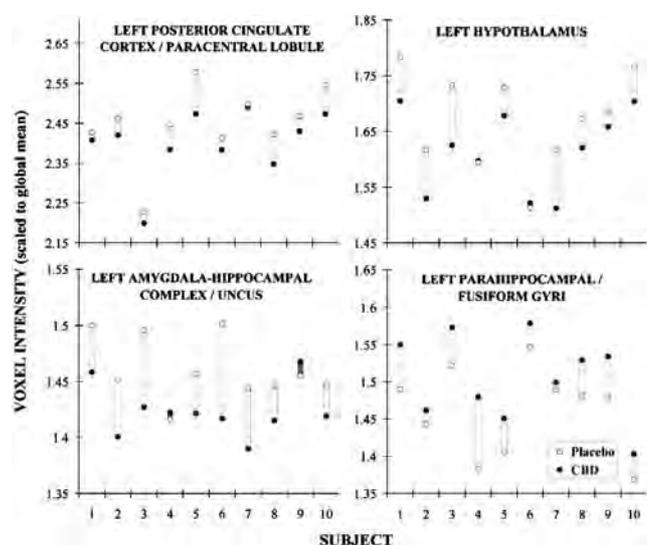


Figure 3 Tracer uptake values during the CBD (filled circle) and PLCB (hollowed circle) conditions are plotted for the 10 subjects, using the voxel of maximal significant difference of each of the four regions reported in Table 1. From left to right and top to bottom: $-4, -27, 47$ (left posterior cingulate cortex/paracentral lobule), $-6, -6, -8$ (left hypothalamus), $-16, -11, -21$ (left amygdala-hippocampal complex), and $-30, -15, -24$ (left parahippocampal/fusiform gyri). Individual values were normalized to the global ECD uptake for each subject and condition. The graphs show that the large majority of individual subjects showed lower ECD activity in the CBD condition relative to the placebo condition in the left amygdala-hippocampus complex, hypothalamus, and posterior cingulate cortex/paracentral lobule, while all subjects had greater ECD uptake in the CBD condition relative to the placebo condition in the left parahippocampal/fusiform gyri.

extending towards the paracentral lobule (BA5/6). At the $p < 0.001$ uncorrected level of significance, this SPM showed additional, unpredicted foci of decreased rCBF in the ECD relative to the placebo condition (> 20 voxels) in the right cerebellum, medial occipital cortex, left inferior temporal, and posterior lateral frontal cortex, but none of these retained significance after correction for multiple comparisons.

Figure 3 displays, for each subject, the magnitude of tracer uptake changes between the CBD and placebo conditions at the voxel of maximal statistical significance in the regions where ECD uptake differences were observed (as summarized in Table 1). All 10 subjects showed greater ECD uptake values in the CBD condition relative to the placebo condition in the left parahippocampal/fusiform gyri. Of the 10 subjects, eight showed lower ECD activity in the CBD condition relative to the placebo condition in the left amygdala-hippocampal complex; eight in the left hypothalamus; and nine in the left posterior cingulate cortex/paracentral lobule (Figure 2). Similar patterns across individual subjects were observed when we used the mean tracer uptake values of all voxels included in the clusters of significant difference between the CBD and placebo conditions (data not shown).

Correlations with Subjective Status Ratings

No correlations were observed between subjective anxiety ratings and ECD uptake in the brain areas where the effects

of CBD had been predicted *a priori* ($p < 0.001$, uncorrected), or in other unpredicted areas after correction for multiple comparisons.

DISCUSSION

When undergoing neuroimaging procedures, such as PET or SPECT, subjects often report increased anxiety before scanning, which is greater than that during or after image acquisition (Grey *et al*, 2000; Gur *et al*, 1987; Giordani *et al*, 1990; Malizia, 1999). The results of the present study showed that a single dose of CBD induced significant decreases in state anxiety before SPECT scanning. Our data thus suggest that this compound has anxiolytic properties, consistent with the results from previous studies in both laboratory animals (Zuardi and Karniol, 1983; Musty *et al*, 1984; Guimaraes *et al*, 1990; Onaivi *et al*, 1990) and humans (Zuardi *et al*, 1982, 1993a).

The anxiolytic effects found in the present study were detected before the anxiety-evoking situation (the tracer injection and scanning procedure), indicating that CBD can affect anticipatory anxiety. In a previous study (Zuardi *et al*, 1993a), the anxiolytic effect of CBD was evident after the stress of public speaking. These antianxiety effects are in contrast to the anxiogenic effects of high doses of Δ^9 -THC (Malit *et al*, 1975; Zuardi *et al*, 1982; Mathew *et al*, 1999), and may help to reconcile apparently conflicting findings obtained with *Cannabis sativa* in relation to anxiety (Johns, 2001; Tournier *et al*, 2003).

Consistent with an anxiolytic effect, we found that CBD significantly modulated resting activity predominantly in limbic and paralimbic cortical areas, which are usually implicated in the pathophysiology of anxiety (Gray, 1982; Graeff, 1994). Thus, between-condition activity differences were detected in a left medial temporal cluster, which included portions of the amygdala and the hippocampus, as well as the hypothalamus, the left posterior cingulate gyrus, and the left parahippocampal gyrus.

The only brain region that showed significantly increased activity in the CBD relative to the placebo condition was the left parahippocampal gyrus. Deactivation of the parahippocampal region in healthy volunteers has been reported after panic attacks induced by lactate (Reiman *et al*, 1989) and CCK-4 (Javanmard *et al*, 1999), and with anxiety induced by presentation of combat-related images (Bremner *et al*, 1999b) and autobiographical memory scripts (Liotti *et al*, 2000). In addition, the abnormal asymmetry of resting activity in the parahippocampal gyri has been associated with panic disorder and with vulnerability to lactate-induced panic (Reiman *et al*, 1984, 1986; Nordahl *et al*, 1990, 1998; Bisaga *et al*, 1998; De Cristofaro *et al*, 1993). These studies suggest that anxiety can be associated with reduced parahippocampal activity, consistent with an anxiolytic effect of CBD and the increased activity in this region that we observed.

In contrast, activity in the left amygdala-hippocampal complex, hypothalamus, and posterior cingulate cortex decreased with CBD relative to placebo. The amygdala is thought to play a key role in mediating fear and anxiety (Deakin and Graeff, 1991; LeDoux, 1998; Gorman *et al*, 2000), being activated during fear conditioning (Furmark

et al, 1997; Morris et al, 1998; LaBar et al, 1998; Buchel et al, 1998), while processing anxious faces (Breiter et al, 1996; Morris et al, 1996; Whalen et al, 1998; Hariri et al, 2002) and during pharmacologically induced anxiety (Ketter et al, 1996; Benkelfat et al, 1995; Servan-Schreiber et al, 1998). Functional and structural changes in the amygdala have also been reported in PTSD (Pitman et al, 2001; Rauch et al, 1996; Shin et al, 1997; Rauch et al, 2000; Liberzon et al, 1999), panic disorder (Uchida et al, 2003; Bystritsky et al, 2001), generalized anxiety disorder (Thomas et al, 2001; De Bellis et al, 2000), and in social (Birbaumer et al, 1998; Tillfors et al, 2001; Furmark et al, 2002) and simple phobias (Wik et al, 1997). The reduction in amygdala activity that we observed with CBD is thus consistent with the anxiolytic effect that it had in our subjects. The hippocampus has also been implicated in the processing of anxiety. Functional neuroimaging studies have shown increased activity in the hippocampus in association with anxiety in OCD (McGuire et al, 1994), panic disorder (Bisaga et al, 1998; Bystritsky et al, 2001; Boshuisen et al, 2002), PTSD (Osuch et al, 2001), and in social phobia (Schneider et al, 1999). However, other studies have reported either decreased or no difference in activity in the hippocampus in association with normal anxiety or anxiety disorders (Schuff et al, 2001; Schneider et al, 1999; Bremner et al, 1997; Fredrikson et al, 1997; Fischer et al, 1996; Paradiso et al, 1997; Liotti et al, 2000).

The hypothalamus is a major component of the central autonomic nervous system, and is often involved in mediating the effects of stress and anxiety (Afifi and Bergman, 1998). Functional imaging studies during fear and anxiety induction in healthy subjects (Fredrikson et al, 1995b; Javanmard et al, 1999) and in panic disorder patients (Boshuisen et al, 2002) have reported increases in the activity of the hypothalamic region, and hypothalamic–pituitary–adrenal axis abnormalities have been commonly reported in anxiety disorders (Hageman et al, 2001). The reduced hypothalamic activity that we observed is thus consistent with the anxiolytic effect of CBD.

The posterior cingulate cortex is strongly linked to temporolimbic structures (Vogt et al, 1992; Maddock, 1999; Afifi and Bergman, 1998), and is thought to play a central role in emotion and anxiety (MacLean, 1993; Maddock, 1999). Increased activity in the posterior cingulate gyrus has been associated with watching anxiety-provoking videos (Fischer et al, 1996; Fredrikson et al, 1995a), and with experimentally provoked obsessions and anxiety in patients with obsessive–compulsive disorder (OCD) (McGuire et al, 1994). Untreated patients with OCD show increased metabolism in the posterior cingulate (Perani et al, 1995) that decreases with treatment, with the change in posterior cingulate rCBF correlated with symptomatic improvement (Rauch et al, 2001, 2002). There have also been reports of increased posterior cingulate activation during symptom provocation in post-traumatic stress disorder (Bremner et al, 1999a) and panic disorder (Bystritsky et al, 2001). However, anxiety induction in phobic patients has been associated with deactivation in the posterior cingulate region (Wik et al, 1993) and Busatto et al (2000) reported a negative correlation between rCBF in the left posterior cingulate cortex and severity of symptoms in OCD.

We did not observe a correlation between the severity of anxiety and rCBF in the areas where activity was modulated by CBD, but this may have been difficult to detect because there was a 15-min gap between the points when the ratings were made and the SPECT tracer was injected.

While the areas where we found modulatory effects of CBD are thus implicated in mediating anxiety, and have also been associated with the anxiolytic effects of diazepam (Di Piero et al, 2001), citalopram (Van der Linden et al, 2000; Furmark et al, 2002), sertraline, and desipramine (Hoehn-Saric et al, 2001), these effects of CBD could be related to an effect other than on anxiety. For instance, we also observed sedative effects of CBD, confirming former findings in animals (Pickens, 1981; Monti, 1977; Colasanti et al, 1984; Zuardi et al, 1981a, 1991) and humans (Carlini et al, 1979; Zuardi et al, 1982, 1993b). This effect has been reported to be dose-related (Pickens, 1981) and CBD has also been shown to decrease wakefulness (Monti, 1977) and to cause longer sleep duration in insomniacs (Carlini and Cunha, 1981). Thus, the reduced hypothalamic activity observed after CBD use in our study could equally be related to sedative effects of CBD, as suggested to occur with other sedative compounds (Tung et al, 2001).

Other pharmacological effects of CBD have been reported in studies in laboratory animals and humans, such as anti-inflammatory (Malfait et al, 2000), anticonvulsant (Carlini et al, 1973; Izquierdo et al, 1973; Cunha et al, 1980), neuroprotective (Hampson et al, 1998), and hormonal effects (Zuardi et al, 1984, 1993a). In addition, the pharmacological profile of CBD is similar to that of clozapine, an ‘atypical’ antipsychotic drug (Zuardi et al, 1991, 1995), and both CBD and clozapine induce *c-fos* expression in the prefrontal cortex and lateral septal nucleus in rats (Zuardi et al, 2001). The mechanism(s) of action whereby CBD produces all these effects remains obscure. This is largely in contrast with the effects of Δ^9 -THC, which mimics the endogenous cannabinoids in many of its actions. CBD does not act through the known cannabinoid receptors, but the stereospecificity previously observed may indicate that CBD binds to another type of receptor in the brain (Mechoulam et al, 2002).

In conclusion, our results suggest that CBD has anxiolytic effects that are mediated through an action on limbic and paralimbic areas of the brain. However, the findings need to be seen as preliminary, given the limitations of the study. Firstly, it would have been desirable to measure plasma levels of CBD and relate them to the magnitude of change in rCBF. Without a dose–response curve, uncertainty about the regional cerebral effects of CBD remains. Nevertheless, it should be pointed out that it is not clear whether there is a relation between plasma levels of cannabinoids—especially CBD—and their clinical effects (Agurell et al, 1986). In addition, the subject sample was modest and the use of SPECT limited the study’s statistical power. Finally, given the limited spatial resolution of the SPECT technique and the smoothing procedure, the interpretation of large foci of tracer uptake changes as involving different brain structures of small size (such as the amygdala, hippocampus, and hypothalamus) should be made with caution. These limitations could be overcome by examining a larger sample and using functional magnetic resonance imaging, which would permit the acquisition of

greater numbers of images with a better spatial and temporal resolution.

ACKNOWLEDGEMENTS

JASC and AWZ are recipients of Conselho Nacional de Desenvolvimento Científico e Tecnológico fellowships (Grants 200984/01-2 and 303770/85-6, respectively). This research was supported in part by the Fundação de Amparo à Pesquisa do Estado de São Paulo fellowship (Grants 02/13197-2, 01/00189-9, 99/12205-7, 99/09547-3, and 95/06195-8). We are grateful to Professor Dr José Antonio Marin Neto (Department of Medical Clinic, University of São Paulo, Ribeirão Preto, Brazil), for technical and logistic assistance. We also thank Professor Dr Frederico G Graeff (Department of Neuropsychiatry and Medical Psychology, University of São Paulo, Ribeirão Preto, Brazil) for comments and suggestions on the manuscript.

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Phil. Trans. R. Soc. B 2012 **367**, 3364-3378
doi: 10.1098/rstb.2011.0389

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Review

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders

Alline Cristina Campos^{1,2}, Fabricio Araújo Moreira³,
Felipe Villela Gomes⁴, Elaine Aparecida Del Bel⁵
and Francisco Silveira Guimarães^{4,*}

¹Group of Neuroimmunology, Laboratory of Immunopharmacology, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

²Infectious Diseases and Tropical Medicine Program, Medical School, and ³Department of Pharmacology, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Avenue Antonio Carlos 6627, 31270-901, Belo Horizonte, Minas Gerais, Brazil

⁴Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo, Avenue Bandeirantes 3900, 14049-900, Ribeirão Preto, São Paulo, Brazil

⁵Faculty of Odontology of Ribeirão Preto, Department of Morphology, Physiology and Stomatology, University of São Paulo, Avenue Café s/n, 14040-904, Ribeirão Preto, São Paulo, Brazil

Cannabidiol (CBD) is a major phytocannabinoid present in the *Cannabis sativa* plant. It lacks the psychotomimetic and other psychotropic effects that the main plant compound Δ^9 -tetrahydrocannabinol (THC) being able, on the contrary, to antagonize these effects. This property, together with its safety profile, was an initial stimulus for the investigation of CBD pharmacological properties. It is now clear that CBD has therapeutic potential over a wide range of non-psychiatric and psychiatric disorders such as anxiety, depression and psychosis. Although the pharmacological effects of CBD in different biological systems have been extensively investigated by *in vitro* studies, the mechanisms responsible for its therapeutic potential are still not clear. Here, we review recent *in vivo* studies indicating that these mechanisms are not unitary but rather depend on the behavioural response being measured. Acute anxiolytic and antidepressant-like effects seem to rely mainly on facilitation of 5-HT_{1A}-mediated neurotransmission in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex. Other effects, such as anti-compulsive, increased extinction and impaired reconsolidation of aversive memories, and facilitation of adult hippocampal neurogenesis could depend on potentiation of anandamide-mediated neurotransmission. Finally, activation of TRPV1 channels may help us to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD. Considering its safety profile and wide range of therapeutic potential, however, further studies are needed to investigate the involvement of other possible mechanisms (e.g. inhibition of adenosine uptake, inverse agonism at CB₂ receptor, CB₁ receptor antagonism, GPR55 antagonism, PPAR γ receptors agonism, intracellular (Ca²⁺) increase, etc.), on CBD behavioural effects.

Keywords: cannabidiol; anxiety; depression; psychosis; serotonin; anandamide

1. HISTORY

Cannabidiol (CBD) is the main non-psychotropic phytocannabinoid present in the *Cannabis sativa* plant, constituting up to 40 per cent of its extract. The chemical characterization of the main cannabinoids present in this plant by Mechoulam's group in the 1960s [1] originated the first wave of scientific interest in this compound. With the discovery of the endocannabinoid (eCB) system in the early 1990s

and the rise, in the words of Bill Devane [2], of the new dawn of cannabinoid pharmacology, there was a renewed interest in CBD, with the number of related published studies growing exponentially since then.

Recent comprehensive reviews suggest that this compound is one of the most promising candidates for a therapeutic tool in a wide range of disorders [3,4]. In the present paper, we will review the evidence that supports its use in psychiatric disorders and the proposal mechanisms that try to explain it.

2. CANNABIDIOL AND ANXIETY

Early reports describing the effects of CBD in animal models of anxiety were inconsistent. Silveira Filho &

* Author for correspondence (fsguimar@fmrp.usp.br).

One contribution of 15 to a Theme Issue 'Endocannabinoids in nervous system health and disease'.

Table 1. Preclinical and clinical studies investigating the anxiolytic properties of CBD. ↓, anxiolytic effect; ↑, anxiogenic effect; CFC, contextual fear conditioning; EPM, elevated plus maze; ETM, elevated T maze; GAD, generalized anxiety patients; OF, open field; VCT, Vogel conflict test; i.p., intraperitoneal injection; i.c.v., intracerebroventricular injection; DPAG, dorsal periaqueductal grey; BNST, bed nucleus of the stria terminalis; PL, prelimbic cortex; IL, infralimbic cortex; CeA, central amygdala.

model	species	effective doses	CBD effect	references
<i>studies with laboratory animals</i>				
Geller-Seifter conflict model	rat	100 mg kg ⁻¹ i.p.	no effect	[5]
conditioned emotional responses	rat	10 mg kg ⁻¹ i.p.	↓	[6]
EPM	rat	2.5–10 mg kg ⁻¹ i.p.	↓	[7]
EPM	mouse	1–10 mg kg ⁻¹ i.p.	↓	[8]
VCT	rat	10 mg kg ⁻¹	↓	[9]
CFC	rat	10 mg kg ⁻¹ i.p.	↓; decreased autonomic responses	[10]
predator exposure (Cat)+ EPM	rat	5 mg kg ⁻¹	↓	[11]
restraint stress + EPM	rat	30 nmol intra-cisterna magna	decreased autonomic and delayed anxiogenic effect	[12]
predator exposure (snake)	mouse	3–30 mg kg ⁻¹ i.p.	panicolytic	[13]
marble burying	mouse	30 mg kg ⁻¹ i.p.	decreased compulsive behaviour	[14]
CFC/fear memory extinction	rat	6.35 nmol i.c.v.	↓; facilitated extinction	[15]
ETM/DPAG electric stimulation	rat	30–60 nmol intra-DPAG	↓, panicolytic	[16]
restraint stress + EPM	rat	10 mg kg ⁻¹ i.p.	decreased autonomic and delayed anxiogenic effect	[17]
EPM/VCT	rat	15–30 nmol intra-DPAG	↓	[18]
EPM/VCT	rat	30–60 nmol intra-BNST	↓	[19]
CFC	rat	30–60 nmol intra-BNST	↓, decreased autonomic responses	[20]
CFC	rat	30 nmol intra-PL	↓	[21]
CFC	rat	30 nmol intra-IL	↑	[21]
CFC	rat	10 mg kg ⁻¹ i.p./daily/14 days	↑	[22]
CFC/fear reconsolidation	rat	10 mg kg ⁻¹ i.p.	↓; memory reconsolidation impairment	[23]
model/measures	subjects	dose (mg, p.o.)	CBD effect	references
<i>clinical studies</i>				
simulated public-speaking	healthy volunteers	400 mg	↓	[24]
neuroimaging study	healthy volunteers	400 mg	↓	[25]
fearful facial stimuli	healthy volunteers	600 mg	↓	[26]
fearful facial stimuli	healthy volunteers	600 mg	↓	[27]
anxiety symptoms (visual analogue mood scale)	GAD	400 mg	↓	[28]
simulated public speaking	social phobics	400 mg	↓	[29]

Tufik [5] did not find any effect of CBD (100 mg kg⁻¹) in rats tested in the classical Geller-Seifter conflict model of anxiety, whereas Zuardi & Karniol [6] described that a much lower CBD dose (10 mg kg⁻¹) attenuated conditioned emotional responses. These apparent contradictory results were subsequently explained by Guimarães *et al.* [7]. Using an ethologically based model of anxiety, the elevated plus maze, they showed that CBD promotes anxiolytic-like effects with an inverted U-shaped dose-response curve, higher doses (more than 20 mg kg⁻¹ in rats) being ineffective (table 1).

The anti-anxiety properties of CBD in rats were later confirmed in different species (mice) and animal models, including the Vogel conflict test and contextual fear conditioning [8–10]. More recently, CBD was shown to decrease defensive behaviours evoked by predator exposure, a proposed model of panic attacks and posttraumatic stress disorder (PTSD) [11,13]. CBD also reduces marble burying behaviour in mice, suggesting that this compound could be effective in obsessive-compulsive disorder (OCD) [14]. Moreover, CBD can interfere in learning and/or memory of aversive events, processes that have

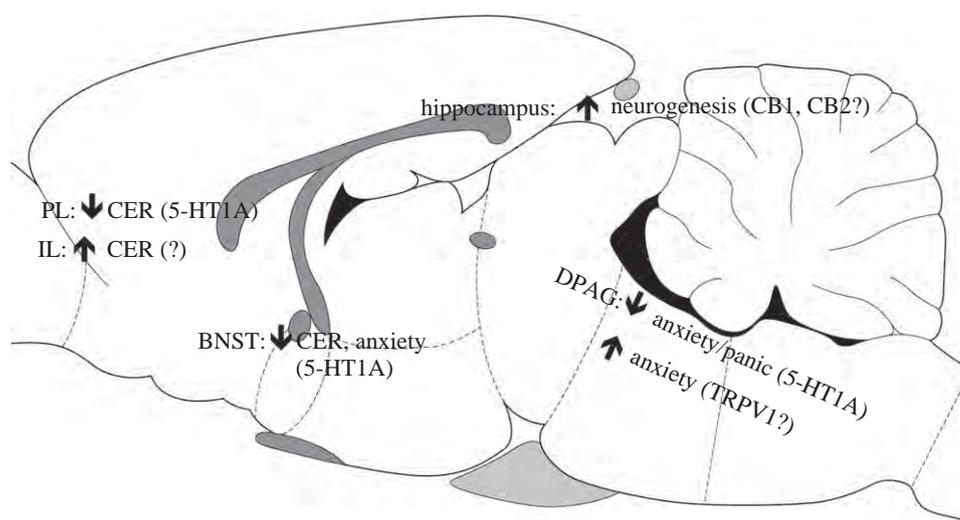


Figure 1. Possible brain sites and mechanisms of CBD effects on anxiety. BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CER, conditioned emotional response; DPAG, dorsal periaqueductal grey; IL, infralimbic prefrontal cortex; PL, prelimbic prefrontal cortex.

been associated with PTSD pathophysiology [30]. Intracerebroventricular administration of CBD facilitates extinction in a contextual aversive conditioning model [15]. In this same paradigm, it can also impair reconsolidation, resulting in the attenuation of the aversive memory trace. In this study, the impairment of contextual fear memory did not show reinstatement and was long-lasting (22 days) [23]. Contrasting with these results, Elbatsh *et al.* [22] have recently reported that repeated (14 days) administration of CBD increases freezing in a contextual fear conditioning test. The reasons for this difference is unknown, but may involve the distinct conditioning protocols and drug administration regime (chronic versus acute) used compared with other studies that investigated the effects of CBD in this model [15,21,23]. Moreover, in this study, it is also possible that CBD could have interfered in learning/memory mechanisms, because the animals were conditioned under the drug effect [22].

(a) *Clinical anxiolytic effects of cannabidiol*

In agreement with the results obtained in animal models, clinical studies confirmed that CBD has anxiolytic properties (table 1). Following the initial report that it blocks the anxiogenic effects of high doses of the main psychoactive compound present in the *Cannabis sativa* plant, Δ^9 -tetrahydrocannabinol (THC) [31], it was demonstrated that CBD can also reduce anxiety in healthy volunteers during a neuroimaging study or after a simulated public-speaking procedure [24,25]. More recently, using the latter procedure, Bergamaschi *et al.* [29] showed that CBD (600 mg p.o.) decreases anxiety in treatment-naïve social phobic patients.

(b) *Brain sites of cannabidiol anxiolytic effects*

Neuroimaging studies show that CBD changes the activity of brain regions related to the control of emotional process [25,27]. It attenuates blood oxygenation in the amygdala and the anterior and posterior cingulate cortex in subjects exposed to fearful faces

[27], impairs the connectivity between the pre-frontal and subcortical regions [27] and decreases the activation of left-amygdala–hippocampal complex and left posterior cingulate gyrus [25].

These clinical findings were complemented by studies in rodents, using direct administration into brain sites related to anxiety- or panic-like responses (figure 1). Microinjection of CBD into the dorsal portions of the periaqueductal grey (DPAG) promoted anxiolytic-like effects in the elevated plus maze, elevated T maze and Vogel conflict tests. It also decreased escape latency in a model of panic attacks, electrical stimulation of the DPAG [16,18]. Anxiolytic effects were also found after CBD injection into the bed nucleus of the *stria terminalis* (BNST) in rats tested in the elevated plus maze, Vogel conflict test and contextual fear conditioning [19,20]. This latter effect corroborates results showing that the effects of CBD in a contextual fear conditioning model is associated with decreased neuronal activation (measure by cFos expression) in this area [21]. This same treatment attenuated the activation of the pre- and infra-limbic cortical regions. In these two brain areas, however, CBD produced opposite effects, decreasing and facilitating, respectively, conditioned emotional responses [10]. Recently, Hsiao *et al.* [26] showed anxiolytic effects of CBD injection into the central nucleus of the amygdala. Other possible brain sites of CBD anxiolytic effect have not yet been investigated (e.g. the hippocampus).

(c) *Mechanisms of the anxiolytic effects of cannabidiol*

CBD can produce multiple pharmacological actions over a wide range of drug concentrations (table 2) [3,4]. CBD is proposed to activate or modify the function of several receptors in the central nervous system (CNS), including CB1, CB2, GPR55, TRPV1 and 5-HT1A receptors (table 2) [32,33,35,42]. Moreover, it could inhibit the anandamide hydrolysing enzyme (fatty acid amide hydrolase, FAAH) and the adenosine

Table 2. Possible mechanisms of CBD behaviour effects. Evidence from *in vitro* studies. CHO, Chinese hamster ovary cells.

biological system	mechanism	biological system	concentration range	references
endocannabinoid/ endovanilloid related mechanisms	CB1 receptor antagonist	mouse brain membranes	4.9 μM (K_i) ^a	[32]
	CB2 receptor inverse agonist	CHO transfected cells	4.2 μM (K_i) ^b	[32]
	TRPV1 agonist	HEK-293 transfected cells	3.2 μM (EC_{50})	[33]
	FAAH/anandamide transporter inhibition	HEK-293 transfected cells, rat brain membranes	7.5–8.6/22 μM (IC_{50})	[33,34]
serotonin-related mechanisms	5-HT1A receptor agonist	CHO transfected cells	16 μM (increases receptor response by 67%)	[35]
	5-HT2A receptor agonist	CHO transfected cells	32 μM (IC_{50})	[35]
	5-HT3 receptor antagonist suppression of mitogen- induced IDO activity (decreasing tryptophan metabolism)	<i>Xenopus laevis</i> oocytes human blood cells	10–30 μM 8.9 μM (IC_{50})	[36] [37]
others	intracellular (Ca^{2+}) increase	hippocampal cell cultures/ hippocampal preparations	approximately 1 μM (effective concentration)	[38,39]
	allosteric modulation of μ and δ opioid receptors	cerebral cortex preparations	100 μM	[40]
	PPAry receptors agonist	aorta preparations	5 μM (IC_{50})	[41]
	GPR55 antagonist	cell membranes of transfected cells	445 nM (IC_{50})	[42]
	blockade of adenosine uptake/indirect A2 agonist	microglia and macrophages cell cultures	less than 250 nM (K_i)/ 500 nM (effective concentration)	[43,44]
	TRPV2 agonist	HEK-293 transfected cells/rat dorsal root ganglia (DRG) sensory neurons	3.7 μM (EC_{50})	[45]
	TRPM8 antagonist	HEK-293 transfected cells/rat dorsal root ganglia (DRG) sensory neurons	80–140 nM (IC_{50})	[46]
	TRPA1 agonist	HEK-293 transfected cells/rat dorsal root ganglia (DRG) sensory neurons	96 nM (EC_{50})	[46]
	P38 MAPKinase inhibition	PC12 cells	10^{-6} – 10^{-4} M (effective concentrations)	[47]
	NF- κ B activation	PC12 cells	10^{-6} – 10^{-4} M (effective concentrations)	[47]
inhibition of mitochondrial superoxide production	vascular endothelial cells	4 μM (effective concentration)	[48]	
inhibition of inducible nitric oxide synthase (iNOS) expression	kidney	10 mg kg^{-1}	[49]	

^aCBD was able to antagonize the effects of the CB1 agonist CP55940-induced stimulation of [³⁵S]GTP γ S binding to mouse brain membranes at a much lower concentration ($K_B = 79$ nM) than the K_i for displacement of the CB1 ligand.

^bCBD acts as an inverse agonist with a lower concentration ($K_B = 65$ nM) than the K_i for displacement of the CB2 ligand.

transporter [33,43,50], indirectly increasing the levels of these neurotransmitters.

Some of CBD effects involve intracellular pathways that play fundamental roles in neuronal physiology. For example, in hippocampal neurons, CBD increases intracellular calcium concentrations via mitochondrial uptake and release and/or activation of type-L voltage-gated calcium channels [38,39]. CBD has also a potent action in inhibiting oxidative and nitrosative stress, a mechanism that has been related to its neuroprotective effects with implications for the treatment of Alzheimer's, Huntington's and Parkinson's

diseases. It decreases the neuronal damage promoted by β -amyloid protein deposit [47,51] and attenuates the depletion of tyrosine hydroxylase, dopamine and GABA levels by modulating the expression of the inducible nitric oxide synthase and reducing the production of reactive oxygen species (ROS)-generating NADPH oxidases [47,52–54]. Moreover, CBD pretreatment attenuated high-glucose-induced mitochondrial superoxide generation and NF- κ B activation, along with the expression of adhesion molecules ICAM-1 and VCAM-1 [48]. Together, these results suggest that CBD can exert CB1- and

CB2-independent neuroprotective/antioxidant/anti-inflammatory effects [48].

The large majority of these possible mechanisms have been unveiled by *in vitro* studies. Their association to the behaviour effects of CBD is still not clear, a topic that is further complicated by the common bell-shaped dose-response curves produced by this compound in distinct biological systems [4].

In the last decade, however, several *in vivo* studies have helped us to understand the mechanisms of CBD central effects.

(d) *In vivo mechanisms of cannabidiol anxiolytic effects: 5-HT1A receptors*

Russo *et al.* [35] were the first to suggest that CBD could act as a 5HT1A receptor agonist. They observed that, at μM range, this drug displaces 8-OH-DPAT, a 5-HT1A receptor agonist, from cloned human 5-HT1A receptors expressed in cultured cells obtained from Chinese hamster ovary. *In vivo* experiments gave further support to the involvement of 5-HT1A receptors in the effects of CBD [18–20,55]. For instance, the neuroprotective effects of CBD in hepatic encephalopathy or cerebral infarction are mediated by these receptors [55,56]. Regarding the behavioural studies, the effects of CBD in a PTSD model (predator exposure) were prevented by WAY100635, a 5HT1A receptor antagonist [11]. This same antagonist prevented the anxiolytic- and panicolytic-like effects of CBD after injections into the DPAG [16,18], bed nucleus of the stria terminalis [19,20] and prefrontal cortex (M. V. Fogaça & F. S. Guimarães 2012, unpublished data; figure 1). In humans, although no study so far has investigated the involvement of 5-HT1A mechanisms in CBD effects, the anxiolytic profile of this drug in the public speaking model was remarkably similar to the positive control ipsapirone, a 5HT1A receptor partial agonist [24].

Other CBD effects also involve 5-HT1A receptors. It decreases nausea and vomiting probably by an indirect agonism at these receptors. Although the mechanism of this indirect action is unclear, it may involve interactions with allosteric sites or changes in different systems that would result in a facilitation of 5-HT1A-mediated responses [57]. Adding to the evidence that the interaction of CBD with 5-HT1A receptors could be complex, it was recently shown that this compound antagonizes food intake induced by 8-OH-DPAT [58]. Therefore, additional research is clearly needed to clarify how CBD facilitates 5-HT1A-mediated neurotransmission.

(e) *In vivo mechanisms of cannabidiol effects: the endocannabinoid system*

CBD could facilitate eCB-mediated neurotransmission by blocking the metabolism and uptake of anandamide [33]. However, AM251, a CB1 receptor antagonist, failed to prevent the anxiolytic effects of CBD injected into the DPAG observed in the elevated plus maze at the same dose that antagonized the anxiolytic effects of anandamide [18,59].

On the other hand, CB1, but not 5-HT1A, receptor antagonism was able to prevent CBD effects on both

extinction and reconsolidation, indicating that its interference on aversive memories involves eCB-mediated mechanisms [15,23]. These results agree with the well-described facilitation of extinction by endogenous cannabinoids [60], suggesting that CBD interferes with aversive memories by facilitating the effects of eCBs [45].

Finally, AM251 blocked CBD effects in the marble burying model [14], whereas 5-HT1A-receptor antagonism was ineffective. This result corroborates the proposal that anxiety and OCD models engage distinct brain mechanisms, with the marble burying behaviour being related to repetitive behaviours instead of anxiety [61].

How facilitation of eCB-mediated neurotransmission decreases repetitive behaviour is unknown, but may involve attenuation of glutamate-mediated neurotransmission. eCBs can reduce the release of several neurotransmitters, including glutamate [62], a major neurotransmitter of the cortico-striato-thalamo-cortical circuitry that has been implicated in the pathophysiology of OCD [63]. Anti-glutamatergic drugs such as riluzole and memantine decrease marble burying behaviour [64,65] and are proposed to be clinically useful for OCD treatment [66,67].

An indirect anti-glutamatergic action via increased eCB neurotransmission may also be involved in other central effects of CBD such as anticonvulsant [3], an effect that could also be related to indirect CB1-mediated inhibition of glutamate release. Corroborating this proposal, anticonvulsant effects of other inhibitors of anandamide metabolism/uptake have recently been described [3]. Moreover, epileptic patients present a significant reduction in the fraction of CB1-positive glutamatergic, but not GABAergic, axon terminals, probably resulting in increased neural excitability [68].

(f) *In vivo mechanisms of cannabidiol effects: adult hippocampal neurogenesis*

Impairment in adult hippocampal neurogenesis has been associated with the pathogenesis of anxiety disorders and depression [69] and at least some of the behavioural effects of prototype antidepressant drugs depend on facilitation of this process [70]. CBD can also increase adult hippocampal neurogenesis, as first demonstrated by Wolf *et al.* [71]. They also showed that the proneurogenic effect of CBD was absent in CB1-knockout mice [71]. Because CBD is not a CB1-receptor agonist, this result suggested that CBD effect was mediated by an indirect activation of these receptors, possibly by inhibition of anandamide metabolism/uptake [33]. Corroborating this latter possibility, recent results from our group showed that CBD increases proliferation of hippocampal progenitor cells in culture, an effect mimicked by CB₁ or CB₂ receptor agonists and prevented by antagonists of these receptors [72]. Moreover, CBD effects were also inhibited by overexpression of the FAAH, reinforcing the proposal of anandamide involvement. These results agree with those previously reported by Jiang *et al.* [73] showing that a synthetic CB1 agonist is able to promote embryonic and adult hippocampus neurogenesis, an effect associated with the anxiolytic

and antidepressant properties of the drug. Similar to prototype antidepressants, the anxiolytic effect of repeated administered CBD (30 mg/daily for 14 days) in mice submitted to a chronic unpredictable stress model disappeared when hippocampal neurogenesis was inhibited [72], suggesting a causal link between its proneurogenic and anxiolytic effect after repeated administration (figure 1).

Other mechanisms could also be involved in CBD effects on adult hippocampal neurogenesis—for example, activation of peroxisome proliferator-activated receptors. This particular mechanism seems to be important during neuroinflammation and neurodegenerative process related to β -amyloid protein deposits in CNS [51]. Although the pro-neurogenic effect of CBD has not yet been studied in rats, it could help us to explain the recent report that repeated CBD treatment enhances contextual fear conditioning [22]. Immature newborn neurons are selectively activated by this task [74], and neurogenesis suppression impairs contextual fear memory [75]. Considering the important role proposed for hippocampal neurogenesis in several brain functions [76,77], the effects and mechanisms of CBD on this process is another important research venue to be pursued.

(g) *Cannabidiol and the vanilloid system*

CBD can activate transient receptor potential (TRP) channels [33]. These channels comprise a family of over 50 members and are present in different species, including yeast, worms, insects, fish and mammals [78]. The vanilloid receptor 1 or TRPV1 is one of the first identified members of the family, being a non-selective cation channel with a preference for calcium. It is activated by noxious stimuli, heat, protons ($\text{pH} < 5.9$) and various, mostly noxious, natural products such as capsaicin [79]. TRPV1 receptors are present in the brain, where anandamide has been proposed to act as an endogenous agonist or an endovanilloid [80]. These receptors can facilitate the release of glutamate [81], a neurotransmitter that induces defensive responses in brain areas such as the DPAG [82]. On the basis of these pieces of evidence, we hypothesized that TRPV1 activation could be at least partially responsible for the inverted U-shaped dose-response curves commonly observed with CBD. Accordingly, using intra-DPAG injections, we showed that local pretreatment with an ineffective dose of the TRPV1 antagonist capsazepine turned a higher, ineffective dose (60 nmol) of CBD into an anxiolytic one [83]. TRPV1 receptors are also involved in the bell-shaped dose responses curves of anandamide analogues [84,85].

In addition to TRPV1, CBD could also interfere with other members of the TRP family, activating TRPV2 and ankyrin type 1 (TRPA1) channels and antagonizing melastatin type 8 (TRPM8) channels [45,46]. The role played by these mechanisms on CBD behavioural effects, however, is unknown at the moment.

3. CANNABIDIOL AND PSYCHOSIS

Initial studies with laboratory animals suggested that CBD prevents some of the effects produced by THC [86]. Similar antagonism was also found in humans,

where CBD attenuated the impairment of time production tasks and the euphoria induced by THC in healthy volunteers [87,88]. Confirming and extending these results, Zuardi *et al.* [31] demonstrated that CBD inhibits THC-induced anxiety and psychotic-like symptoms such as disconnected thoughts, perceptual disturbance, depersonalization and resistance to communication. In the same year, it was observed that patients admitted to a psychiatric hospital in South Africa after the use of a variety of *Cannabis* virtually devoid of CBD showed a much higher frequency of acute psychotic episodes than in other countries [89], suggesting that the presence of CBD in *Cannabis* samples protects users against the occurrence of THC-induced acute psychotic episodes. Because experimental evidence indicates that the antagonistic effect of CBD did not result from a pharmacokinetic interaction between the two cannabinoids [90], these initial observations led to the hypothesis that CBD could possess antipsychotic properties.

An initial study in rats investigated whether this compound could attenuate stereotypies induced by the dopaminergic agonist apomorphine. CBD effects were compared with those of haloperidol [91]. Both drugs reduced apomorphine-induced stereotyped behaviour in a dose-related manner. Even though they increased plasma levels of prolactin, CBD had much lower potency, with significant increases only seen after the doses of 120 and 240 mg kg⁻¹. Moreover, contrary to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg kg⁻¹. These results suggest that CBD exhibits a profile similar to atypical antipsychotic drugs. In another study, CBD was compared with haloperidol and clozapine, an atypical antipsychotic drug. The drug inhibited the hyperlocomotion induced by amphetamine and ketamine, an NMDA receptor antagonist, in mice [92]. As expected, while both haloperidol and clozapine inhibited hyperlocomotion, only haloperidol induced catalepsy. These results extend CBD antipsychotic-like effects to a glutamate-based model. In agreement with these results, CBD, similar to clozapine, reversed the disruption of prepulse inhibition (PPI) in mice and the hyperactivity and reduction of social interaction in rats caused by MK-801, another NMDA receptor antagonist [93,94]. Typical antipsychotics, on the other hand, are usually unable to restore the deficits in PPI and social interaction induced by NMDA receptor antagonists [95,96].

Extending findings from studies using single drug administration, chronic treatment with CBD attenuated amphetamine-induced hyperlocomotion [97]. Preliminary results from our group indicate that this treatment regime is also able to decrease the impairments in PPI and object recognition induced by repeated administration of MK-801 (F. V. Gomes, E. A. Del Bel & F. S. Guimarães, unpublished data). Despite these findings, there are also negative results regarding the possible antipsychotic effects of CBD. Chronic treatment with this drug failed to change behavioural changes such as locomotor hyperactivity and PPI deficits observed in transmembrane domain neuregulin 1 mutant (Nrg1) mice, a proposed model for a schizophrenia susceptibility gene [98]. A summary of

Table 3. Preclinical and clinical studies investigating the antipsychotic properties of CBD. ↓, antipsychotic-like effects; BPRS, brief psychiatric rating scale; CADSS, clinician administered dissociative states scale; PANSS, positive and negative syndrome scale; PPQ, Parkinson psychosis questionnaire.

model	species	effective doses	CBD effects	references
<i>studies with laboratory animals</i>				
apomorphine-induced stereotyped behaviour	rat	60 mg kg ⁻¹	↓	[91]
D-amphetamine- and ketamine-induced hyperlocomotion	mouse	15–60 mg kg ⁻¹	↓	[92]
MK-801-induced disruption of PPI	mouse	5 mg kg ⁻¹	↓	[93]
D-amphetamine-induced hyperlocomotion	mouse	50 mg kg ⁻¹ (chronic – 21 days)	↓	[97]
MK-801-induced social withdrawal and disruption of PPI	rat	3–30 mg kg ⁻¹	↓	[99]
MK-801-induced hyperlocomotion and deficits in social interaction and locomotor hyperactivity and PPI	rat	3 mg kg ⁻¹	↓	[94]
locomotor hyperactivity and PPI	<i>Nrg 1</i> mutant mouse	1, 50 and 100 mg kg ⁻¹	no effects	[98]
model/measures	subjects (<i>n</i>)	doses	CBD effects	references
<i>clinical studies</i>				
THC-induced impairment of time production task	healthy male volunteers (40)	15–60 mg (acute)	↓	[87]
THC-induced euphoria	healthy male volunteers (15)	0.15 mg kg ⁻¹ (inhalation; acute)	↓	[88]
THC-induced psychotic symptoms	healthy male volunteers (eight)	1 mg kg ⁻¹ (acute)	↓	[31]
nabilone-induced impairment of perception of binocular depth inversion	healthy male volunteers (nine)	200 mg (acute)	↓	[100]
THC-induced psychotic symptoms (PANSS)	healthy male and female volunteers (six)	5 mg (iv, acute)	↓	[101]
ketamine-induced psychotic symptoms (BPRS and CADSS)	healthy male volunteers (10)	600 mg (acute)	↓ (trend)	[102]
psychotic symptoms (BPRS)	schizophrenic female patient (one)	increasing oral doses of CBD, reaching 1500 mg d ⁻¹ (four weeks)	↓	[103]
psychotic symptoms (BPRS)	male patients with treatment-resistant schizophrenia (three)	increased from 40 up to 1280 mg d ⁻¹ (30 days)	one patient showed mild improvement	[104]
L-dopa-induced psychosis (BPRS and PPQ)	Parkinson's disease patients (six)	increased from 150 up to 600 mg d ⁻¹ depending on the clinical response (four weeks)	↓	[105]
psychotic symptoms (BPRS and PANSS)	acute paranoid schizophrenia patients (42)	600 mg d ⁻¹ (four weeks)	↓	[34]
Stroop Colour Word Test	schizophrenic patients (28)	300 and 600 mg (acute)	no effect	[106]

the studies investigating the antipsychotic-like effects of CBD in animal models can be seen in table 3.

(a) *Cannabidiol and psychosis: clinical studies*

The antipsychotic-effects of CBD have also been demonstrated in humans (table 3). In healthy volunteers, Leweke *et al.* [100] observed that the decrease of the perception of illusory image induced by nabilone, a synthetic cannabinoid drug with THC-like properties,

was reduced by CBD. Another model used to evaluate antipsychotic-like activity of drugs in humans is the administration of sub-anaesthetic doses of ketamine. This drug induces psychotic symptoms that mimic both positive and negative symptoms of schizophrenia. An initial investigation in healthy subjects showed that CBD induced a non-significant trend to reduce ketamine-induced dissociative effects, but, at the same time, augmented the activating effects of ketamine

[102]. Because only a single dose of CBD was used, additional studies are needed to characterize the effects of CBD in this model [102].

The therapeutic use of CBD in psychotic patients was tested for the first time in 1995. In an open, case-report study, a 19-year-old black schizophrenic female patient, who presented serious side effects after treatment with conventional antipsychotics, received increasing oral doses of CBD (up to 1500 mg d⁻¹) for four weeks [103]. A significant improvement with no side effects was observed in all items of the standard brief psychiatric rating scale (BPRS) during CBD treatment, with an efficacy similar to that of haloperidol. Symptom worsening was observed when the administration was interrupted. In another case study, CBD was administered to three 22- or 23-year-old male schizophrenic patients who had not responded to typical antipsychotic drugs for 30 days [104]. The dose of CBD was increased from 40 up to 1280 mg d⁻¹. One patient showed mild improvement, but only slight or no change was observed in the other two, suggesting that CBD may not be effective for the treatment of resistant schizophrenia. Moreover, CBD had no beneficial effects on the performance of schizophrenic patients in the Stroop colour word test, which can be used to assess attentional processes frequently impaired in schizophrenia [106]. It is still unknown whether chronic administration of CBD could improve the cognitive deficits in the disorder. No significant side effects were observed during CBD treatment in these clinical studies, suggesting that CBD is safe and well tolerated in schizophrenic patients.

In an open-label study evaluating CBD effects on psychotic symptoms associated with L-dopa use in Parkinson's patients [105], the drug decreased scores of a questionnaire developed to assess psychotic symptoms in Parkinson's disease (Parkinson psychosis questionnaire), improved total BPRS scores as well as scores specifically related to positive and negative symptoms. Confirming the lack of motor effects observed in animal studies, CBD did not affect motor function. On the contrary, it decreased the total scores of the unified Parkinson's disease rating scale, suggesting an improvement of this function.

Overall, therefore, even if there are negative results, most clinical studies with normal subjects or schizophrenic patients suggest that CBD has antipsychotic properties. Corroborating this possibility, a four-week double-blind controlled clinical trial in 42 acute schizophrenic and schizophreniform psychosis patients comparing the effects of CBD with those of amisulpride, an atypical antipsychotic, showed that both treatments were equally effective in reducing acute psychotic symptoms after two and four weeks of treatment [34]. Moreover, compared with amisulpride, CBD caused a lower incidence of extrapyramidal symptoms and increases in prolactin and weight gain.

The presence of antipsychotic properties in CBD is also supported by convergent evidence linking the habitual use of *Cannabis* to the risk of developing schizophrenia or schizophrenia-like psychosis, especially in vulnerable subjects [107]. This effect has been attributed to THC. In agreement with the initial reports showing antagonism of THC-induced psychotomimetic

effects [31,87,88], the presence of CBD in *Cannabis* strains has been shown to be protective against the occurrence of psychotic-like reactions and cognitive impairment [108–110]. In this context, Di Forti *et al.* [111] found that the use of *Cannabis* containing high THC- and low CBD concentration was associated with a higher risk of a first psychotic episode. Furthermore, the presence of CBD protects from *Cannabis*-associated decrease in hippocampal volume [112]. This neuroprotective effect of CBD has also been reported in the human basal ganglia, where there was a strong positive correlation between *N*-acetylaspartate/total creatine ratio and the amount of CBD (as measured by its presence in hair samples) in the putamen/globus pallidum of recreational *Cannabis* users. This finding could reflect a CBD-induced enhancement of neuronal and axonal integrity in these regions [113]. More recently, Bhattacharyya *et al.* [114], investigating the effects of THC and CBD during attentional salience processing, have also showed that these two cannabinoids produce opposite effects on prefrontal, striatal and hippocampal functions.

(b) Brain sites and mechanisms of cannabidiol antipsychotic effects

Few studies in laboratory animals have investigated the possible brain sites and mechanisms of CBD antipsychotic effects. Consistent with the behavioural data described earlier, both CBD and clozapine, but not haloperidol, increased neuronal activation (measured by cFos-protein expression) in the prefrontal cortex. Probably reflecting its motor side effects, only haloperidol increased cFos in the dorsal striatum. CBD, and, in addition, increased cFos in the nucleus accumbens [115], an effect shared by typical and atypical antipsychotic drugs [116]. Intracerebroventricular administration of CBD (10 µg) also enhanced cFos expression in waking-related brain areas such as hypothalamus and dorsal raphe nucleus [117], but the relation between this finding and its antipsychotic properties is unclear.

A number of neuroimaging studies in healthy volunteers have compared the effects of CBD and high doses of THC. Consistent with the behavioural findings in humans and rodents, these drugs caused opposite effects on brain activity in the striatum, anterior cingulate, prefrontal cortex, parahippocampal gyrus, amygdala, right posterior superior temporal gyrus, middle occipital gyrus and cerebellum [27, 101,114,118–120]. Behavioural measurements in these studies indicated that some of these changes (decreased activation of ventral and dorsal striatum, anterior cingulate gyrus, right temporal lobe) are associated with the psychotic-like effects of THC, suggesting that these regions could be possible brain sites of CBD action [121]. No study using direct injections into key brain regions associated with the pathophysiology of schizophrenia, such as the prefrontal cortex and nucleus accumbens, has been performed so far to investigate CBD antipsychotic properties.

Regarding the pharmacological mechanisms, intracerebroventricular administration of CBD enhanced extracellular levels of dopamine in the nucleus accumbens [122]. A similar finding was found after

Table 4. Antidepressant-like effects of CBD. Studies with laboratory animals. FST, forced swimming test; TST, tail suspension test.

model	species	effective doses	CBD effects	references
restraint stress	rat	10–20 mg kg ⁻¹	↓ cardiovascular and behavioural effects of stress	[17]
FST	mouse	200 mg kg ⁻¹	↓ immobility	[127]
TST	mouse	20–200 mg kg ⁻¹	no effect	[127]
FST	mouse	30 mg kg ⁻¹	↓ immobility	[128]
chronic unpredictable stress	mouse	30 mg kg ⁻¹ (daily, chronic treatment)	↓ the behavioural consequences of stress through enhancement of hippocampal neurogenesis	[72]

microdialysis perfusion of CBD (30, 60 or 90 nM) into the rat lateral hypothalamus [117], a procedure that also enhanced alertness. It is unclear how this effect would relate to the antipsychotic properties of CBD because usual antipsychotic drugs act by antagonizing dopamine-2 receptors [123]. Moreover, studies with animal models that involve dopaminergic stimulation suggest that the antipsychotic-like doses of CBD (60–120 mg kg⁻¹) are higher than those needed to induce anxiolytic-like effects [7,91,92] and reverse behavioural deficits induced by the NMDA receptor antagonist MK-801 [93,94,99]. These findings indicate that the mechanisms of CBD effects on glutamate- or dopamine-based models could be at least partially distinct. This possibility needs to be further explored.

Recently, Leweke *et al.* [34] showed that schizophrenic patients treated with CBD present higher anandamide serum levels compared with those receiving the antipsychotic amisulpride. Moreover, in the CBD group, there was a significant association between anandamide levels and improvement of psychotic symptoms. In the same study, they confirmed, *in vitro*, that CBD inhibits FAAH activity in a concentration (10 μ M) that does not interact with receptors (dopamine, GABA, serotonin and glutamate) commonly associated with schizophrenia. However, by indirectly activating CB1 receptors via increased levels of anandamide, CBD could potentially modulate neurotransmitters systems related to these receptors [121, 124]. Moreover, as previously discussed, facilitation of CB1-mediated neurotransmission by CBD also increases adult hippocampal neurogenesis, a mechanism that could be related to the cognitive deficits found in schizophrenic patients [124].

As discussed already, CBD and anandamide can also activate TRPV1 channels. This mechanism, probably by facilitating the pre-synaptic release of glutamate [80], is involved in the ability of CBD to reverse the disruption of PPI induced by the NMDA receptor antagonist MK-801 [93].

Other mechanisms that could also help us to explain CBD anti-psychotic effects are facilitation of 5-HT_{1A}-mediated neurotransmission, an effect shared by the atypical anti-psychotic aripiprazole, which acts as a partial agonist at these receptors, and anti-inflammatory/neuroprotective action [124].

4. CANNABIDIOL AND DEPRESSION

Cannabis sativa exerts significant effects upon humour, which include euphoria and mood elevation [125].

THC may account for most of these effects through activation of CB1 receptors. Considering these observations, as well as the effects of synthetic cannabinoids and drugs that increase eCB levels, a putative role for the eCB system in mood disorders has been proposed [126]. The effects of CBD, however, have been scarcely investigated (table 4). The fact that this compound, in addition to facilitating eCB activity [33], may facilitate the activation of 5-HT_{1A} receptors [35] suggests that it might also have antidepressant-like properties. 5HT_{1A} receptors modulate responses to stressful stimuli and are proposed to mediate the effects of antidepressant drugs [129].

Stress exposure is a key aetiological factor in depression [130] and animal models used to study antidepressant-like effects are generally based on acute responses to inescapable aversive stimuli, which are prevented by antidepressants [131]. Alternatively, considering the nature of depression as a chronic psychiatric disorder, some models investigate drug effects upon the diverse consequences of chronic stress, including anhedonia and changes in exploratory activity [132].

One of the first studies that indicate the presence of antidepressant-like properties in CBD focused on its ability to prevent the autonomic and behavioural consequences of inescapable stress [17]. Rats were submitted to restraint stress during 60 min, which increases heart rate and blood pressure and caused anxiogenic-like responses in rats exposed to the elevated plus maze 24 h later. CBD was injected 30 min before the stress at the doses of 1, 10 or 20 mg kg⁻¹. The doses of 10 and 20 mg kg⁻¹ attenuated the changes in autonomic parameters, whereas at 10 mg kg⁻¹ CBD also prevented the late anxiogenic-like effect of stress. There were no changes in motor activity or basal cardiovascular parameters, discarding any possible confounding factor [17]. Similar effects were observed after intra-cisterna magna administration of CBD [12], thus suggesting that these effects are centrally mediated.

Another behavioural model widely used to assess antidepressant-like effects, mainly due to its pharmacological predictability, is the forced swim test. In this assay, rats or mice exposed to inescapable swimming assume a posture of immobility, which is reversed by antidepressants [131]. We tested in mice the effects of CBD (3–100 mg kg⁻¹) injected 30 min prior to the test [128]. The drug produced an inverted U-shaped dose-response curve. At the dose of 30 mg kg⁻¹, it reduced immobility similar to the tricyclic antidepressant imipramine (30 mg kg⁻¹). Our behavioural

findings in the forced swimming test were confirmed by another study, published in the same year. CBD was tested at the doses of 20, 100 and 200 mg kg⁻¹ [127], with the higher dose being effective. The drug had no effect, however, in the mouse tail suspension test. One drawback common to all these studies is that the animals received only acute injections. Depression, however, is a chronic disorder that requires long-lasting drug treatment [130]. CBD has been recently tested against the consequences of chronic unpredictable stress, which includes anhedonia and anxiety-like behaviour [130]. Chronic treatment with CBD was able to prevent these behavioural changes, an effect that depends on hippocampal neurogenesis, similar to antidepressant drugs [72]. This observation further strengthens the notion that this natural cannabinoid should be considered as a potential approach for the treatment of mood disorders.

Despite this body of evidence, no clinical study has investigated whether CBD can decrease depressive symptoms in patients. This compound has been tested, however, in patients suffering from bipolar disorders, a subtype of mood disorder, in whom it was not effective in treating manic episodes [133]. Actually, this is in line with animal models, in which CBD failed to prevent hyperactivity in rodents [134].

To summarize, although the data are scarce, preclinical studies so far do provide evidence that this compound could induce antidepressant-like effects. Clinical studies are important to confirm this possibility.

(a) Mechanisms of cannabidiol antidepressant effects

Similar to findings with animal models of anxiety, the attenuation of the behavioural consequences of restraint stress and the antidepressant-like effects of CBD in the forced swimming test were attenuated by a 5-HT_{1A} receptor antagonist [17,128]. In the latter model, despite the association between increased expression of neurotrophic factors and antidepressant activity [130], CBD failed to modify brain-derived neurotrophic factor hippocampal levels [128].

As discussed earlier, CBD can also facilitate hippocampal neurogenesis, probably by facilitation of eCB neurotransmission [72]. The involvement of this mechanism on its antidepressant-like properties after repeated administration remains to be investigated.

5. CONCLUSIONS

CBD is a safe compound with a wide range of therapeutic applications, including the treatment of psychiatric disorders [3,4]. These findings make this drug an attractive candidate for future clinical use. Its therapeutic use, however, has some limiting factors. In addition to its low and variable oral bioavailability in humans [135], it causes bell-shaped dose-response curves and, judging from the studies with laboratory animals, possesses a narrow therapeutic dose range. A clear target of future research, therefore, is to try to develop compounds with similar safety and clinical profile but with larger effective dose ranges. To this aim, a better understanding of the mechanisms responsible for the unique properties of CBD is essential.

The behaviour studies reviewed here clearly indicate that more than one mechanism is involved, depending on the effects being measured (anxiolytic, anti-compulsive, antidepressant or antipsychotic-like) and the drug regime (single versus repeated administration). Facilitation of 5-HT_{1A}-mediated neurotransmission in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex, seems responsible for CBD acute anxiolytic-like effects. Other CBD effects, such as anti-compulsive, increased extinction and impaired reconsolidation of aversive memories, facilitation of adult hippocampal neurogenesis and blockade of the anxiogenic consequences of chronic unpredictable stress could depend on potentiation of anandamide-mediated neurotransmission. Finally, activation of TRPV1 channels may help us to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD. In addition to these mechanisms, CBD can interfere in several other important biological processes (e.g. inhibition of adenosine uptake, inverse agonism at CB₂ receptor, CB₁ receptor antagonism, GPR55 antagonism, PPAR γ receptors agonism, intracellular (Ca²⁺) increase, etc.). Additional *in vivo* studies are clearly needed to investigate their possible involvement on CBD behavioural effects.

This work was supported by grants from CNPq, CAPES, NAPNA-USP and FAPESP.

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Cannabidiol as a Potential Treatment for Anxiety Disorders

Esther M. Blessing¹ · Maria M. Steenkamp¹ · Jorge Manzanares^{1,2} · Charles R. Marmar¹

Published online: 4 September 2015

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Abstract Cannabidiol (CBD), a *Cannabis sativa* constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

Keywords Cannabidiol · Endocannabinoids · Anxiety · Generalized anxiety disorder · Post-traumatic stress disorder

✉ Esther M. Blessing
esther.blessing@nyumc.org

¹ New York University School of Medicine, New York, NY, USA

² Instituto de Neurociencias de Alicante, Universidad Miguel Hernández and Consejo Superior de Investigaciones Científicas, Alicante, Spain

Introduction

Fear and anxiety are adaptive responses essential to coping with threats to survival. Yet excessive or persistent fear may be maladaptive, leading to disability. Symptoms arising from excessive fear and anxiety occur in a number of neuropsychiatric disorders, including generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), and obsessive–compulsive disorder (OCD). Notably, PTSD and OCD are no longer classified as anxiety disorders in the recent revision of the Diagnostic and Statistical Manual of Mental Disorders-5; however, excessive anxiety is central to the symptomatology of both disorders. These anxiety-related disorders are associated with a diminished sense of well-being, elevated rates of unemployment and relationship breakdown, and elevated suicide risk [1–3]. Together, they have a lifetime prevalence in the USA of 29 % [4], the highest of any mental disorder, and constitute an immense social and economic burden [5, 6].

Currently available pharmacological treatments include serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressant drugs, and partial 5-hydroxytryptamine (5-HT)_{1A} receptor agonists. Anticonvulsants and atypical antipsychotics are also used to treat PTSD. These medications are associated with limited response rates and residual symptoms, particularly in PTSD, and adverse effects may also limit tolerability and adherence [7–10]. The substantial burden of anxiety-related disorders and the limitations of current treatments place a high priority on developing novel pharmaceutical treatments.

Cannabidiol (CBD) is a phytocannabinoid constituent of *Cannabis sativa* that lacks the psychoactive effects of Δ^9 -tetrahydrocannabinol (THC). CBD has broad therapeutic properties across a range of neuropsychiatric disorders, stemming from diverse central nervous system actions [11, 12]. In recent

years, CBD has attracted increasing interest as a potential anxiolytic treatment [13–15]. The purpose of this review is to assess evidence from current preclinical, clinical, and epidemiological studies pertaining to the potential risks and benefits of CBD as a treatment for anxiety disorders.

Methods

A search of MEDLINE (PubMed), PsycINFO, Web of Science Scopus, and the Cochrane Library databases was conducted for English-language papers published up to 1 January 2015, using the search terms “cannabidiol” and “anxiety” or “fear” or “stress” or “anxiety disorder” or “generalized anxiety disorder” or “social anxiety disorder” or “social phobia” or “post-traumatic stress disorder” or “panic disorder” or “obsessive compulsive disorder”. In total, 49 primary preclinical, clinical, or epidemiological studies were included. Neuroimaging studies that documented results from anxiety-related tasks, or resting neural activity, were included. Epidemiological or clinical studies that assessed CBD’s effects on anxiety symptoms, or the potential protective effects of CBD on anxiety symptoms induced by cannabis use (where the CBD content of cannabis is inferred via a higher CBD:THC ratio), were included.

CBD Pharmacology Relevant to Anxiety

General Pharmacology and Therapeutic Profile

Cannabis sativa, a species of the *Cannabis* genus of flowering plants, is one of the most frequently used illicit recreational substances in Western culture. The 2 major phyto-cannabinoid constituents with central nervous system activity are THC, responsible for the euphoric and mind-altering effects, and CBD, which lacks these psychoactive effects. Preclinical and clinical studies show CBD possesses a wide range of therapeutic properties, including antipsychotic, analgesic, neuroprotective, anti-convulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties (see [11, 12, 16–19] for reviews). A review of potential side effects in humans found that CBD was well tolerated across a wide dose range, up to 1500 mg/day (orally), with no reported psychomotor slowing, negative mood effects, or vital sign abnormalities noted [20].

CBD has a broad pharmacological profile, including interactions with several receptors known to regulate fear and anxiety-related behaviors, specifically the cannabinoid type 1 receptor (CB₁R), the serotonin 5-HT_{1A} receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor [11, 12, 19, 21]. In addition, CBD may also regulate, directly or indirectly, the peroxisome proliferator-activated receptor- γ , the orphan G-protein-coupled receptor 55, the equilibrative nucleoside transporter, the adenosine transporter,

additional TRP channels, and glycine receptors [11, 12, 19, 21]. In the current review of primary studies, the following receptor-specific actions were found to have been investigated as potential mediators of CBD’s anxiolytic action: CB₁R, TRPV1 receptors, and 5-HT_{1A} receptors. Pharmacology relevant to these actions is detailed below.

The Endocannabinoid System

Following cloning of the endogenous receptor for THC, namely the CB₁R, endogenous CB₁R ligands, or “endocannabinoids” (eCBs) were discovered, namely anandamide (AEA) and 2-arachidonoylglycerol (reviewed in [22]). The CB₁R is an inhibitory G_{i/o} protein-coupled receptor that is mainly localized to nerve terminals, and is expressed on both γ -aminobutyric acid-ergic and glutamatergic neurons. eCBs are fatty acid derivatives that are synthesized on demand in response to neuronal depolarization and Ca²⁺ influx, via cleavage of membrane phospholipids. The primary mechanism by which eCBs regulate synaptic function is retrograde signaling, wherein eCBs produced by depolarization of the postsynaptic neuron activate presynaptic CB₁Rs, leading to inhibition of neurotransmitter release [23]. The “eCB system” includes AEA and 2-arachidonoylglycerol; their respective degradative enzymes fatty acid amide hydroxylase (FAAH) and monoacylglycerol lipase; the CB₁R and related CB₂ receptor (the latter expressed mainly in the periphery); as well as several other receptors activated by eCBs, including the TRPV1 receptor, peroxisome proliferator-activated receptor- γ , and G protein-coupled 55 receptor, which functionally interact with CB₁R signaling (reviewed in [21, 24]). Interactions with the TRPV1 receptor, in particular, appear to be critical in regulating the extent to which eCB release leads to inhibition or facilitation of presynaptic neurotransmitter release [25]. The TRPV1 receptor is a postsynaptic cation channel that underlies sensation of noxious heat in the periphery, with capsaicin (hot chili) as an exogenous ligand. TRPV1 receptors are also expressed in the brain, including the amygdala, periaqueductal grey, hippocampus, and other areas [26, 27].

The eCB system regulates diverse physiological functions, including caloric energy balance and immune function [28]. The eCB system is also integral to regulation of emotional behavior, being essential to forms of synaptic plasticity that determine learning and response to emotionally salient, particularly highly aversive events [29, 30]. Activation of CB₁Rs produces anxiolytic effects in various models of unconditioned fear, relevant to multiple anxiety disorder symptom domains (reviewed in [30–33]). Regarding conditioned fear, the effect of CB₁R activation is complex: CB₁R activation may enhance or reduce fear expression, depending on brain locus and the eCB ligand [34]; however, CB₁R activation potentially enhances fear extinction [35], and can prevent fear reconsolidation. Genetic manipulations that impede

CB₁R activation are anxiogenic [35], and individuals with eCB system gene polymorphisms that reduce eCB tone—for example, FAAH gene polymorphisms—exhibit physiological, psychological, and neuroimaging features consistent with impaired fear regulation [36]. Reduction of AEA–CB₁R signaling in the amygdala mediates the anxiogenic effects of corticotropin-releasing hormone [37], and CB₁R activation is essential to negative feedback of the neuroendocrine stress response, and protects against the adverse effects of chronic stress [38, 39]. Finally, chronic stress impairs eCB signaling in the hippocampus and amygdala, leading to anxiety [40, 41], and people with PTSD show elevated CB₁R availability and reduced peripheral AEA, suggestive of reduced eCB tone [42].

Accordingly, CB₁R activation has been suggested as a target for anxiolytic drug development [15, 43, 44]. Proposed agents for enhancing CB₁R activation include THC, which is a potent and direct agonist; synthetic CB₁R agonists; FAAH inhibitors and other agents that increase eCB availability, as well as nonpsychoactive cannabis phytocannabinoids, including CBD. While CBD has low affinity for the CB₁R, it functions as an indirect agonist, potentially via augmentation of CB₁R constitutional activity, or via increasing AEA through FAAH inhibition (reviewed in [21]).

Several complexities of the eCB system may impact upon the potential of CBD and other CB₁R-activating agents to serve as anxiolytic drugs. First, CB₁R agonists, including THC and AEA, have a biphasic effect: low doses are anxiolytic, but higher doses are ineffective or anxiogenic, in both preclinical models in and humans (reviewed in [33, 45]). This biphasic profile may stem from the capacity of CB₁R agonists to also activate TRPV1 receptors when administered at a high, but not low dose, as demonstrated for AEA [46]. Activation of TRPV1 receptors is predominantly anxiogenic, and thus a critical balance of eCB levels, determining CB₁ *versus* TRPV1 activation, is proposed to govern emotional behavior [27, 47]. CBD acts as a TRPV1 agonist at high concentrations, potentially by interfering with AEA inactivation [48]. In addition to dose-dependent activation of TRPV1 channels, the anxiogenic *versus* anxiolytic balance of CB₁R agonists also depends on dynamic factors, including environmental stressors [33, 49].

5-HT_{1A} Receptors

The 5-HT_{1A} receptor (5-HT_{1A}R) is an established anxiolytic target. Buspirone and other 5-HT_{1A}R agonists are approved for the treatment of GAD, with fair response rates [50]. In preclinical studies, 5-HT_{1A}R agonists are anxiolytic in animal models of general anxiety [51], prevent the adverse effects of stress [52], and enhance fear extinction [53]. Both pre- and postsynaptic 5-HT_{1A}Rs are coupled to various members of the G_{i/o} protein family. They are expressed on serotonergic neurons in the raphe, where they exert autoinhibitory function, and

various other brain areas involved in fear and anxiety [54, 55]. Mechanisms underlying the anxiolytic effects of 5-HT_{1A}R activation are complex, varying between both brain region, and pre- *versus* postsynaptic locus, and are not fully established [56]. While in vitro studies suggest CBD acts as a direct 5-HT_{1A}R agonist [57], in vivo studies are more consistent with CBD acting as an allosteric modulator, or facilitator of 5-HT_{1A} signaling [58].

Preclinical Evaluations

Generalized Anxiety Models

Relevant studies in animal models are summarized in chronological order in Table 1. CBD has been studied in a wide range of animal models of general anxiety, including the elevated plus maze (EPM), the Vogel-conflict test (VCT), and the elevated T maze (ETM). See Table 1 for the anxiolytic effect specific to each paradigm. Initial studies of CBD in these models showed conflicting results: high (100 mg/kg) doses were ineffective, while low (10 mg/kg) doses were anxiolytic [59, 60]. When tested over a wide range of doses in further studies, the anxiolytic effects of CBD presented a bell-shaped dose–response curve, with anxiolytic effects observed at moderate but not higher doses [61, 90]. All further studies of acute systemic CBD without prior stress showed anxiolytic effects or no effect [62, 65], the latter study involving intracerebroventricular rather than the intraperitoneal route. No anxiogenic effects of acute systemic CBD dosing in models of general anxiety have yet been reported. As yet, few studies have examined chronic dosing effects of CBD in models of generalized anxiety. Campos et al. [66] showed that in rat, CBD treatment for 21 days attenuated inhibitory avoidance acquisition [83]. Long et al. [69] showed that, in mouse, CBD produced moderate anxiolytic effects in some paradigms, with no effects in others.

Anxiolytic effects of CBD in models of generalized anxiety have been linked to specific receptor mechanisms and brain regions. The midbrain dorsal periaqueductal gray (DPAG) is integral to anxiety, orchestrating autonomic and behavioral responses to threat [91], and DPAG stimulation in humans produces feelings of intense distress and dread [92]. Microinjection of CBD into the DPAG produced anxiolytic effects in the EPM, VGC, and ETM that were partially mediated by activation of 5-HT_{1A}Rs but not by CB₁Rs [65, 68]. The bed nucleus of the stria terminalis (BNST) serves as a principal output structure of the amygdaloid complex to coordinate sustained fear responses, relevant to anxiety [93]. Anxiolytic effects of CBD in the EPM and VCT occurred upon microinjection into the BNST, where they depended on 5-HT_{1A}R

Table 1 Preclinical studies

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Silveira Filho et al. [59]	WR	i.p.	100 mg/kg , acute	GSCT	No effect	NA
Zuardi et al. [60]	WR	i.p.	10 mg/kg , acute	CER	Anxiolytic	NA
Onaivi et al. [61]	ICR mice	i.p.	0.01, 0.10, 0.50 , 1.00 , 2.50 , 5.00 , 10.00 , 50.00 , 100.00 mg/kg, acute	EPM	Anxiolytic	Effects ↓ by IP flumazenil, unchanged by naloxone
Guimaraes et al. [61]	WR	i.p.	2.5 , 5.0 , 10.0 and 20.0 mg/kg, acute	EPM	Anxiolytic	NA
Moreira et al. [62]	WR	i.p.	2.5, 5.0 and 10.0 mg/kg, acute	VCT	Anxiolytic	Effect unchanged by IP flumazenil
Ressel et al. [63]	WR	i.p.	10 mg/kg, acute	CFC	Anxiolytic	NA
Campos et al. [64]	WR	dIPAG	15.0, 30.0 , 60.0 nmol/0.2 µl, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra-dIPAG WAY100635 but not intra-dIPAG AM251
Bitencourt et al. [65]	WR	i.c.v.	2.0 µg/µl 5 min before extinction, acute	CFC extinction EPM before and 24 h after CFC	Anxiolytic No effect before CFC Anxiolytic following CFC	Extinction effect ↓ by SR141716A but not capsazepine
Campos et al. [66]	WR	dIPAG	30 , 60 mg/kg, acute	EPM	Anxiolytic	Intra-dIPAG capsazepine renders 60 mg/kg anxiolytic
Ressel et al. [67]	WR	i.p.	1, 10 or 20 mg/kg, acute	RS	Anxiolytic, ↓ Pressor ↓ Tachycardia Anxiolytic	All effects ↓ by systemic WAY100635
Soares et al. [68]	WR	dIPAG	15, 30 or 60 nmol, acute	EPM 24 h following RS ETM	Anxiolytic Panicolytic Panicolytic	All effects ↓ by intra-dIPAG WAY100635 but not AM251
Long et al. [69]	C57BL/6 J mice	i.p.	1, 5, 10, 50 mg/kg, chronic, daily/21 d	PAG E-stim EPM L-DT	No effect 1 mg/kg anxiolytic	NA
Lemos et al. [70]	WR	i.p. PL IL	10 mg/kg IP, 30 nmol intra-PL and intra-IL, acute	SI OF CFC	No effect 50 mg/kg anxiolytic IP and PL anxiolytic IL angiogenic	NA
Casarotto et al. [71]	C57BL/6 J mice	i.p.	15, 30 , and 60 mg/kg, acute, or subchronic, daily/7 d	MBT	Anticompulsive	Effect ↓ by IP/AM251 but not WAY100635
Gomes et al. [72]	WR	BNST	15, 30 , and 60 nmol, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra BNST WAY100635
Granjeiro et al. [73]	WR	Intracisternal	15, 30 , and 60 nmol, acute	RS EPM 24 h after RS	Anxiolytic, ↓ Pressor ↓ Tachycardia Anxiolytic	NA
Deiana et al. [74]	SM	i.p. Oral	120 mg/kg, acute	MBT	Anticompulsive	NA
Uribe-Marino et al. [75]	SM	i.p.	0.3, 3.0 , 30.0 mg/kg, acute	PS	Panicolytic	NA

Table 1 (continued)

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Stern et al. [76]	WR	i.p.	3, 10, 30 mg/kg immediately after retrieval, acute	Reconsolidation blockade	Anxiolytic 1 and 7 d old fear memories disrupted	Effect ↓ by AM251 but not WAY100635
Campos et al. [77]	WR	i.p.	5 mg/kg , subchronic, daily/7 d	EPM following PS	Anxiolytic	Effects ↓ by IP WAY100635
Hsiao et al. [78]	WR	CeA	1 μg/μl	REM sleep time EPM	↓ REM sleep suppression Anxiolytic	NA
Gomes et al. [79]	WR	BNST	15, 30, 60 nmol , acute	OF CFC	Anxiolytic Anxiolytic	Both effects ↓ by intra-BNST WAY100635
El Baïsh et al. [80]	LE-HR	i.p.	10 mg/kg , chronic, daily/14 d	CFC	Anxiogenic	NA
Campos et al. [81]	C57BL/6 mice	i.p.	30 mg/kg 2 h after CUS, chronic daily/14 d	EPM NSF	Anxiolytic Anxiolytic	Both effects ↓ by AM251
Do Monte et al. [82]	L-E HR	IL	1 μg or 0.4 μg/0.2 μl 5 min before extinction daily/4 d	Extinction of CFC	Anxiolytic	Effect ↓ by IP rimonabant
Campos et al. [83]	Rat	i.p.	5 mg/kg , chronic, daily/21 d	ETM	Anxiolytic Panicolytic	Panicolytic effect ↓ by intra-dIPAG WAY100635
Almeida et al. [84]	Rat	i.p.	1, 5, 15 mg/kg , acute	SI	Anxiolytic	NA
Gomes et al. [85]	WR	BNST	30 and 60 nmol , acute	RS	Anxiogenic ↑ Tachycardia	Effect ↓ by WAY100635
Twardowschy et al. [86]	SM	i.p.	3 mg/kg , acute	PS	Panicolytic	Effects ↓ by IP WAY100635
Focageta et al. [87]	WR	PL	15, 30, 60 nmol , acute	EPM EPM after RS CFC	Anxiogenic Anxiolytic Anxiolytic	All effects ↓ by intra PL WAY100635 Anxiolytic EPM effect post-RS ↓ by IP metyrapone
Nardo et al. [88]	SM	i.p.	30 mg/kg , acute	MBT	Anticompulsive	NA
da Silva et al. [89]	WR	SNpr	5 μg/0.2 μl	GABA _A blockade in dISC	Panicolytic	Both effects ↓ by AM251

Effective doses are in bold

Receptor specific agents: AM251 = cannabinoid receptor type 1 (CB₁R) inverse agonist; WAY100635 = 5-hydroxytryptamine 1A antagonist; SR141716A = CB₁R antagonist; rimonabant = CB₁R antagonist; capsazepine = transient receptor potential vanilloid type 1 antagonist; naloxone = opioid antagonist; flumazenil = GABA_A receptor antagonist

Anxiolytic effects in models used: CER = reduced fear response; CFC = reduced conditioned freezing; CFC extinction = reduced freezing following extinction training; EPM = reduced % time in open arm; ETM = decreased inhibitory avoidance; L-DT = increased % time in light; VCT = increased licks indicating reduced conflict; NSF = reduced latency to feed; OF = increased % time in center; SI = increased social interaction

Anticompulsive effects: MBT = reduced burying

Panicolytic effects: ETM = decreased escape; GABA_A blockade in dISC = defensive immobility, and explosive escape; PAG-E-Stim = increased threshold for escape; PS = reduced explosive escape
WR = Wistar rats; SM = Swiss mice; L-E HR = Long-Evans hooded rats; i.p. = intraperitoneal; dIPAG = dorsolateral periaqueductal gray; i.c.v. = intracerebroventricular; PL = prelimbic; IL = infralimbic; BNST = bed nucleus of the stria terminalis; CeA = amygdala central nucleus; SNpr = substantia nigra pars reticularis; CUS = chronic unpredictable stress; GSCT = Geller-Seifter conflict test; CER = conditioned emotional response; EPM = elevated plus maze; VCT = Vogel conflict test; CFC = contextual fear conditioning; RS = restraint stress; ETM = elevated T maze; PAG E-stim = electrical stimulation of the dIPAG; L-DT = light-dark test; SI = social interaction; OF = open field; MBT = marble-burying test; PS = predator stress; NSF = novel suppressed feeding test; GABA_A = γ-aminobutyric acid receptor A; dISC = deep layers superior colliculus; REM = rapid eye movement; NA = not applicable

activation [79], and also upon microinjection into the central nucleus of the amygdala [78]. In the prelimbic cortex, which drives expression of fear responses via connections with the amygdala [94], CBD had more complex effects: in unstressed rats, CBD was anxiogenic in the EPM, partially via 5-HT_{1A}R receptor activation; however, following acute restraint stress, CBD was anxiolytic [87]. Finally, the anxiolytic effects of systemic CBD partially depended on GABA_A receptor activation in the EPM model but not in the VCT model [61, 62].

As noted, CBD has been found to have a bell-shaped response curve, with higher doses being ineffective. This may reflect activation of TRPV1 receptors at higher dose, as blockade of TRPV1 receptors in the DPAG rendered a previously ineffective high dose of CBD as anxiolytic in the EPM [66]. Given TRPV1 receptors have anxiogenic effects, this may indicate that at higher doses, CBD's interaction with TRPV1 receptors to some extent impedes anxiolytic actions, although was notably not sufficient to produce anxiogenic effects.

Stress-induced Anxiety Models

Stress is an important contributor to anxiety disorders, and traumatic stress exposure is essential to the development of PTSD. Systemically administered CBD reduced acute increases in heart rate and blood pressure induced by restraint stress, as well as the delayed (24 h) anxiogenic effects of stress in the EPM, partially by 5-HT_{1A}R activation [67, 73]. However intra-BNST microinjection of CBD *augmented* stress-induced heart rate increase, also partially via 5-HT_{1A}R activation [85]. In a subchronic study, CBD administered daily 1 h after predator stress (a proposed model of PTSD) reduced the long-lasting anxiogenic effects of chronic predator stress, partially via 5-HT_{1A}R activation [77]. In a chronic study, systemic CBD prevented increased anxiety produced by chronic unpredictable stress, in addition to increasing hippocampal AEA; these anxiolytic effects depended upon CB₁R activation and hippocampal neurogenesis, as demonstrated by genetic ablation techniques [81]. Prior stress also appears to *modulate* CBD's anxiogenic effects: microinjection of CBD into the prelimbic cortex of unstressed animals was anxiogenic in the EPM but following restraint stress was found to be anxiolytic [87]. Likewise, systemic CBD was anxiolytic in the EPM following but not prior to stress [65].

PD and Compulsive Behavior Models

CBD inhibited escape responses in the ETM and increased DPAG escape electrical threshold [68], both proposed models of panic attacks [95]. These effects partially depended on 5-HT_{1A}R activation but were not affected by CB₁R blockade. CBD was also panicolytic in the predator–prey model, which

assesses explosive escape and defensive immobility in response to a boa constrictor snake, also partially via 5-HT_{1A}R activation; however, more consistent with an anxiogenic effect, CBD was also noted to decrease time spent outside the burrow and increase defensive attention (not shown in Table 1) [75, 86]. Finally, CBD, partially via CB₁Rs, decreased defensive immobility and explosive escape caused by bicuculline-induced neuronal activation in the superior colliculus [89]. Anticompulsive effects of CBD were investigated in marble-burying behavior, conceptualized to model OCD [96]. Acute systemic CBD reduced marble-burying behavior for up to 7 days, with no attenuation in effect up to high (120 mg/kg) doses, and effect shown to depend on CB₁Rs but not 5-HT_{1A}Rs [71, 74, 88].

Contextual Fear Conditioning, Fear Extinction, and Reconsolidation Blockade

Several studies assessed CBD using contextual fear conditioning. Briefly, this paradigm involves pairing a neutral context, the conditioned stimulus (CS), with an aversive unconditioned stimulus (US), a mild foot shock. After repeated pairings, the subject learns that the CS predicts the US, and subsequent CS presentation elicits freezing and other physiological responses. Systemic administration of CBD prior to CS re-exposure reduced conditioned cardiovascular responses [63], an effect reproduced by microinjection of CBD into the BNST, and partially mediated by 5-HT_{1A}R activation [79]. Similarly, CBD in the prelimbic cortex reduced conditioned freezing [70], an effect prevented by 5-HT_{1A}R blockade [87]. By contrast, CBD microinjection in the infralimbic cortex *enhanced* conditioned freezing [70]. Finally, El Batsh et al. [80] reported that repeated CBD doses over 21 days, that is chronic as opposed to acute treatment, *facilitated* conditioned freezing. In this study, CBD was administered prior to conditioning rather than prior to re-exposure as in acute studies, thus further directly comparable studies are required.

CBD has also been shown to enhance extinction of contextually conditioned fear responses. Extinction training involves repeated CS exposure in the absence of the US, leading to the formation of a new memory that inhibits fear responses and a decline in freezing over subsequent training sessions. Systemic CBD administration immediately before training markedly enhanced extinction, and this effect depended on CB₁R activation, without involvement of TRPV1 receptors [65]. Further studies showed CB₁Rs in the infralimbic cortex may be involved in this effect [82].

CBD also blocked reconsolidation of aversive memories in rat [76]. Briefly, fear memories, when reactivated by re-exposure (retrieval), enter into a labile state in

which the memory trace may either be reconsolidated or extinguished [97], and this process may be pharmacologically modulated to achieve reconsolidation blockade or extinction. When administered immediately following retrieval, CBD prevented freezing to the conditioned context upon further re-exposure, and no reinstatement or spontaneous recovery was observed over 3 weeks, consistent with reconsolidation blockade rather than extinction [76]. This effect depended on CB₁R activation but not 5-HT_{1A}R activation [76].

Summary and Clinical Relevance

Overall, existing preclinical evidence strongly supports the potential of CBD as a treatment for anxiety disorders. CBD exhibits a broad range of actions, relevant to multiple symptom domains, including anxiolytic, panicolytic, and anticomulsive actions, as well as a decrease in autonomic arousal, a decrease in conditioned fear expression, enhancement of fear extinction, reconsolidation blockade, and prevention of the long-term anxiogenic effects of stress. Activation of 5-HT_{1A}Rs appears to mediate anxiolytic and panicolytic effects, in addition to reducing conditioned fear expression, although CB₁R activation may play a limited role. By contrast, CB₁R activation appears to mediate CBD's anticomulsive effects, enhancement of fear extinction, reconsolidation blockade, and capacity to prevent the long-term anxiogenic consequences of stress, with involvement of hippocampal neurogenesis.

While CBD predominantly has acute anxiolytic effects, some species discrepancies are apparent. In addition, effects may be contingent on prior stress and vary according to brain region. A notable contrast between CBD and other agents that target the eCB system, including THC, direct CB₁R agonists and FAAH inhibitors, is a lack of anxiogenic effects at a higher dose. Further receptor-specific studies may elucidate the receptor specific basis of this distinct dose response profile. Further studies are also required to establish the efficacy of CBD when administered in chronic dosing, as relatively few relevant studies exist, with mixed results, including both anxiolytic and anxiogenic outcomes.

Overall, preclinical evidence supports systemic CBD as an acute treatment of GAD, SAD, PD, OCD, and PTSD, and suggests that CBD has the advantage of not producing anxiogenic effects at higher dose, as distinct from other agents that enhance CB₁R activation. In particular, results show potential for the treatment of multiple PTSD symptom domains, including reducing arousal and avoidance, preventing the long-term adverse effects of stress, as well as enhancing the extinction and blocking the reconsolidation of persistent fear memories.

Human Experimental and Clinical Studies

Evidence from Acute Psychological Studies

Relevant studies are summarized in Table 2. The anxiolytic effects of CBD in humans were first demonstrated in the context of reversing the anxiogenic effects of THC. CBD reduced THC-induced anxiety when administered simultaneously with this agent, but had no effect on baseline anxiety when administered alone [99, 100]. Further studies using higher doses supported a lack of anxiolytic effects at baseline [101, 107]. By contrast, CBD potently reduces experimentally induced anxiety or fear. CBD reduced anxiety associated with a simulated public speaking test in healthy subjects, and in subjects with SAD, showing a comparable efficacy to ipsapirone (a 5-HT_{1A}R agonist) or diazepam [98, 105]. CBD also reduced the presumed anticipatory anxiety associated with undergoing a single-photon emission computed tomography (SPECT) imaging procedure, in both healthy and SAD subjects [102, 104]. Finally, CBD enhanced extinction of fear memories in healthy volunteers: specifically, inhaled CBD administered prior to or after extinction training in a contextual fear conditioning paradigm led to a trend-level enhancement in the reduction of skin conductance response during reinstatement, and a significant reduction in expectancy (of shock) ratings during reinstatement [106].

Evidence from Neuroimaging Studies

Relevant studies are summarized in Table 3. In a SPECT study of resting cerebral blood flow (rCBF) in normal subjects, CBD reduced rCBF in left medial temporal areas, including the amygdala and hippocampus, as well as the hypothalamus and left posterior cingulate gyrus, but increased rCBF in the left parahippocampal gyrus. These rCBF changes were not correlated with anxiolytic effects [102]. In a SPECT study, by the same authors, in patients with SAD, CBD reduced rCBF in overlapping, but distinct, limbic and paralimbic areas; again, with no correlations to anxiolytic effects [104].

In a series of placebo-controlled studies involving 15 healthy volunteers, Fusar-Poli et al. investigated the effects of CBD and THC on task-related blood-oxygen-level dependent functional magnetic resonance imaging activation, specifically the go/no-go and fearful faces tasks [109, 110]. The go/no-go task measures response inhibition, and is associated with activation of medial prefrontal, dorsolateral prefrontal, and parietal areas [111]. Response activation is diminished in PTSD and other anxiety disorders, and increased activation predicts response to treatment [112]. CBD produced no changes in predicted areas (relative to placebo) but reduced activation in the left insula, superior temporal gyrus, and transverse temporal gyrus. The fearful faces task activates the amygdala, and other medial temporal areas involved in

Table 2 Human psychological studies

Study	Subjects, design	CBD route, dose	Measure	Effect
Karniol et al. [99]	HV, DBP	Oral, 15, 30, 60 mg, alone or with THC, acute, at 55, 95, 155, and 185 min	Anxiety and pulse rate after THC and at baseline	↓ THC-induced increases in subjective anxiety and pulse rate No effect at baseline
Zuardi et al., [100]	HV, DBP	Oral 1 mg/kg alone or with THC, acute, 80 min	STAI score after THC	↓ THC-induced increases in STAI scores
Zuardi et al. [98]	HV, DBP	Oral 300 mg, acute, 80 min	VAMS, STAI and BP following SPST	↓ STAI scores ↓ VAMS scores ↓ BP
Martin-Santos et al. [101]	HV, DBP	Oral 600 mg, acute, 1, 2, 3 h	Baseline anxiety and pulse rate	No effect
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	VAMS before SPECT	↓ VAMS scores
Bhattacharyya et al. [103]	15 HV, DBP	Oral 600 mg, acute, 1, 2, 3 h	STAI scores VAMS scores	↓ STAI scores ↓ VAMS scores
Crippa et al. [104]	SAD and HC, DBP	Oral 400 mg, acute, 75 and 140 min	VAMS before SPECT	↓ VAMS scores
Bergamaschi et al. [105]	SAD and HC, DBP	Oral 600 mg, acute, 1, 2, 3 h	VAMS, SSPS-N, cognitive impairment, SCR, HR after SPST	↓ VAMS, SSPS-N and cognitive impairment, no effect on SCR or HR
Das et al. [106]	HV, DBP	Inhaled, 32 mg, acute, immediately following, before, after extinction	SCR and shock expectancy following extinction	CBD after extinction training produced trend level reduction in SCR and decreased shock expectancy
Hindocha et al. [107]	Varying in schizotypy and cannabis use, DBP	Inhaled, 16 mg, acute	Baseline VAS anxiety	No significant effect of CBD

HV = healthy volunteers; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; THC = Δ^9 -tetrahydrocannabinol; STAI = Spielberger's state trait anxiety inventory; VAMS = visual analog mood scale; BP = blood pressure; SPST = simulated public speaking test; SCR = skin conductance response; SPECT = single-photon emission computed tomography; SSPS-N = negative self-evaluation subscale; HR = heart rate; VAS = visual analog scale, CBD = cannabidiol

Table 3 Neuroimaging studies

Study	Subjects, design	CBD route, dose, timing	Measure	Effect of CBD
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	SPECT, resting (rCBF)	↓ rCBF in left medial temporal cluster, including amygdala and HPC, also ↓ rCBF in the HYP and posterior cingulate gyrus ↑ rCBF in left PHG
Borgwardt et al. [108]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI during oddball and go/no-go task	↓ Activation in left insula, STG and MTG
Fusar-Poli et al. [109]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI activation during fearful faces task	↓ Activation in left medial temporal region, including amygdala and anterior PHG, and in right ACC and PCC
Fusar-Poli et al. [110]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI functional connectivity during fearful faces task	↓ Functional connectivity between L) AMY and ACC
Crippa et al. [104]	SAD and HC, DBP	Oral 400 mg, acute, 75 and 140 min	SPECT, resting (rCBF)	↓ rCBF in the left PHG, HPC and ITG. ↑ rCBF in the right posterior cingulate gyrus

CBD = cannabidiol; HV = healthy controls; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; SPECT = single-photon emission computed tomography; rCBF = regional cerebral blood flow; fMRI = functional magnetic resonance imaging; HPC = hippocampus; HYP = hypothalamus; PHG = parahippocampal gyrus; STG = superior temporal gyrus; MTG = medial temporal gyrus; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex

emotion processing, and heightened amygdala response activation has been reported in anxiety disorders, including GAD and PTSD [113, 114]. CBD attenuated blood-oxygen-level dependent activation in the left amygdala, and the anterior and posterior cingulate cortex in response to intensely fearful faces, and also reduced amplitude in skin conductance fluctuation, which was highly correlated with amygdala activation [109]. Dynamic causal modeling analysis in this data set further showed CBD reduced forward functional connectivity between the amygdala and anterior cingulate cortex [110].

Evidence from Epidemiological and Chronic Studies

Epidemiological studies of various neuropsychiatric disorders indicate that a higher CBD content in chronically consumed cannabis may protect against adverse effects of THC, including psychotic symptoms, drug cravings, memory loss, and hippocampal gray matter loss [115–118] (reviewed in [119]). As THC acutely induces anxiety, this pattern may also be evident for chronic anxiety symptoms. Two studies were identified, including an uncontrolled retrospective study in civilian patients with PTSD patients [120], and a case study in a patient with severe sexual abuse-related PTSD [121], which showed that chronic cannabis use significantly reduces PTSD symptoms; however, these studies did not include data on the THC:CBD ratio. Thus, overall, no outcome data are currently available regarding the chronic effects of CBD in the treatment of anxiety symptoms, nor do any data exist regarding the potential protective effects of CBD on anxiety potentially induced by chronic THC use.

Summary and Clinical Relevance

Evidence from human studies strongly supports the potential for CBD as a treatment for anxiety disorders: at oral doses ranging from 300 to 600 mg, CBD reduces experimentally induced anxiety in healthy controls, without affecting baseline anxiety levels, and reduces anxiety in patients with SAD. Limited results in healthy subjects also support the efficacy of CBD in acutely enhancing fear extinction, suggesting potential for the treatment of PTSD, or for enhancing cognitive behavioral therapy. Neuroimaging findings provide evidence of neurobiological targets that may underlie CBD's anxiolytic effects, including reduced amygdala activation and altered medial prefrontal amygdala connectivity, although current findings are limited by small sample sizes, and a lack of independent replication. Further studies are also required to establish whether chronic, in addition to acute CBD dosing is anxiolytic in human. Also, clinical findings are currently limited to SAD, whereas preclinical evidence suggests CBD's potential to treat multiple symptom domains relevant to GAD, PD, and, particularly, PTSD.

Conclusions

Preclinical evidence conclusively demonstrates CBD's efficacy in reducing anxiety behaviors relevant to multiple disorders, including PTSD, GAD, PD, OCD, and SAD, with a notable lack of anxiogenic effects. CBD's anxiolytic actions appear to depend upon CB₁Rs and 5-HT_{1A}Rs in several brain regions; however, investigation of additional receptor actions may reveal further mechanisms. Human experimental findings support preclinical findings, and also suggest a lack of anxiogenic effects, minimal sedative effects, and an excellent safety profile. Current preclinical and human findings mostly involve acute CBD dosing in healthy subjects, so further studies are required to establish whether chronic dosing of CBD has similar effects in relevant clinical populations. Overall, this review emphasizes the potential value and need for further study of CBD in the treatment of anxiety disorders.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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Original Article

Cannabis Use in HIV for Pain and Other Medical Symptoms

Emily Woolridge, MB BS, BSc, Simon Barton, MB BS (Distinction), BSc, FRCP (Ed), FRCP (London), Jonathon Samuel, BSc, Jess Osorio, BSc, Andrew Dougherty, BSc, and Anita Holdcroft, MB ChB, MD, FRCA

Magill Department of Anesthesia, Imperial College London (E.W., A.H.), and HIV/GUM Services (S.B., J.S., J.O., A.D.), Chelsea and Westminster Hospital, London, United Kingdom

Abstract

*Despite the major benefits of antiretroviral therapy on survival during HIV infection, there is an increasing need to manage symptoms and side effects during long-term drug therapy. Cannabis has been reported anecdotally as being beneficial for a number of common symptoms and complications in HIV infections, for example, poor appetite and neuropathy. This study aimed to investigate symptom management with cannabis. Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration. Symptom control using cannabis is widespread in HIV outpatients. A large number of patients reported that cannabis improved symptom control. *J Pain Symptom Manage* 2005;29:358–367. © 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Cannabis, HIV, pain, symptoms

Introduction

HIV or AIDS affects over 40 million people in the world¹ and more than 49,500 in the UK.² Although there is still no cure available for this disease, remarkable improvements in the survival of HIV-infected individuals have been achieved.³ This survival has led to an increasing prevalence of individuals with HIV infection, many on long-term treatment with combinations

of antiretroviral therapies. This has increased the clinical focus on the management of chronic symptoms associated with both HIV and the side effects of antiretroviral medication. Recently, in small sample studies of HIV patients, the medicinal use of cannabis has been documented as a treatment for varied symptoms.^{4–7}

Symptoms associated with HIV occur as both direct and indirect consequences of the disease process and as a side effect of the antiretroviral drugs used in the treatment of the disease. These symptoms include nausea and vomiting, pain (e.g., in a nerve distribution), reduced appetite, weight loss, headaches, diarrhea, constipation, anxiety, and depression. Flu-like symptoms and severe myalgia can result directly

Address reprint requests to: Anita Holdcroft, MB ChB, Magill Department of Anesthesia, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom.

Accepted for publication: July 28, 2004.

from seroconversion early in the disease. Central pain and peripheral neuropathy can occur as a result of viral-mediated neurotoxicity, secondary to either mitochondrial damage, demyelination, or low B₁₂ levels, all of which have been observed in patients with HIV. The inflammation that occurs as a result of the mitochondrial damage can result in HIV-related encephalopathy or HIV-related colitis. Symptoms may also occur secondary to infections or tumors, which have resulted from HIV-related immunosuppression. Examples of this include nausea and dysphagia from esophageal candida, or pain from a gastrointestinal lymphoma. Symptoms commonly occurring as a side effect of HIV treatment include renal colic from nephrolithiasis associated with the protease inhibitor, indinavir; painful peripheral neuropathy from use of stavudine, a nucleoside analogue; or sleep disturbances from the non-nucleoside inhibitor, efavirenz. Thus, a wide range of symptoms can significantly affect the quality of life of individuals living with HIV as a long-term chronic infection.^{8,9}

It has been recognized that cannabinoids such as delta-9-tetrahydrocannabinol (THC), which is now available as a licensed pharmaceutical preparation, can improve appetite and relieve nausea and vomiting.¹⁰ Cannabis plant material not only contains THC but also other cannabinoids, such as cannabidiol (CBD), that may mitigate psychotic mood effects of THC.¹¹

The aim of this study was to measure the patterns and prevalence of cannabis use in patients presenting at a large HIV clinic and to evaluate its beneficial or detrimental effect on symptom control.

Methods

Subjects

Following Ethics Committee approval, HIV-positive patients were recruited into an anonymous cross-sectional questionnaire survey using a single center. The outpatient clinic provided a walk-in service as well as pre-arranged appointments, including pharmacy and phlebotomy sections. All patients entering the clinic were asked to verbally consent to participate in the study. Written consent was not obtained in order to protect patient anonymity. The number of patients who refused to take part

was recorded. Many patients were regular clinic users, had discussed their symptoms with HIV and pain specialists, and were able to distinguish between the various types of pain described on the questionnaire. A researcher was available to answer questions (e.g., on the interpretation of words). Patients completed the questionnaire while waiting and confidentiality was maintained by enumerating the papers without patient identification.

Questionnaire

The questionnaire was piloted to refine its content, word use, and format and then issued to patients attending the clinic. The questionnaire (see Appendix) was designed to contain close-ended questions with defined yes/no or categorical responses. It was divided into sections. The first included demographics (age, sex, number of years with HIV) and a validated scale to measure degree of disability described by Sharrack and Hughes.¹² The second had specific questions concerning the patient's use of cannabis medically to treat symptoms of HIV. These symptoms included those directly related to HIV plus those resulting from their medication. Those who did not use cannabis for medicinal purposes, including those who used it solely for recreation, were not required to continue completing the questionnaire, although their demographic details were recorded. The next section included questions relating to frequency, patterns, and reasons for cannabis use. Then in tabular form, a range of symptoms were listed (Table 1), and against

Table 1
Order of Symptom List in Questionnaire as Scored by Patients for Benefit or Detriment

Lack of appetite
Feeling sick (i.e., nausea)
Tremor
Depression
Anxiety
Weight loss
Weakness
Tiredness
Vision dimness
Slurred speech
Memory loss
Constipation
Headaches
Diarrhea
Pain in muscles
Nerve pain
Tingling
Numbness

each one, the patient was invited to score benefit or detriment as 'much better,' 'little better,' 'unchanged,' 'a little worse,' and 'much worse'. For the symptoms of pain and sensory changes, the questionnaire also contained 'body diagrams', that is, pain maps, so that the patients could mark where they identified their nerve or muscle pain, tingling and numbness.

Analysis

Data from the questionnaires were entered into an Access database (Windows 98 version) and analyzed using the Statistical Package for Social Sciences (SPSS 11.5, SPSS Inc., Chicago). Categorical data comparing the sex differences between the two groups and symptom severity were analyzed using the Fisher's exact test. Because the distribution of age and the number of years with HIV were not normal and had some outliers, the differences in these variables between the two groups were analyzed using the Mann-Whitney U test. Both simple frequency analysis and the sign test were used in assessing the percentage improvement or deterioration in symptoms.

Results

A total of 523 questionnaires were completed from 565 patients approached. This was a 93% response rate. Of those who completed the study, 143 (27%) used cannabis to treat symptoms associated with HIV.

Physical Data

The sex, age, years with HIV, disability, and cannabis user status are shown in Tables 2 and 3.

About 1 in 10 patients were female and few were severely disabled in this outpatient setting. Compared with females, males were statistically significantly likely to be cannabis users ($P < 0.01$) and those who had the disease for longer and were more disabled were also more likely to be users ($P < 0.01$).

When nerve pain was reported on the pain map, it was experienced mainly in the legs, and less in the feet and hands (27, 19, and 15 patients, respectively). Muscle pain was predominantly localized to the legs, but also to the lower back, shoulders and neck (46, 19, and 19 patients, respectively). Tingling and numbness was experienced in the periphery, with the hands and feet being affected (34 and 26 patients, respectively).

Patient Choice of Route and Timing for Symptom Control

Of the 143 patients who had used cannabis to treat HIV symptoms, 107 (75%) were current users. Within the whole group, smoking was the single route of administration in 101 (71%), and was combined with eating and drinking the plant in 39 (27%); ingestion was the only route in 3 (2%). On a day that cannabis was used, 50 patients (36%) would take it once, 33 (23%) twice, 23 (16%) three times, and 35 (24%) four or more times. Most patients (79/143 [55%]) were daily users and 15 (11%) used it weekly. Others reported intermittent administration during the week. Thus, all patients reported using cannabis at least once a week to relieve symptoms.

Throughout the day, the majority of patients (91/143 [64%]) took cannabis after 6 p.m. and

Table 2
Demographic Data, Disability Scores, and the Number of Patients Using Cannabis to Treat Symptoms

	Females $n = 43$ (8%)	Males $n = 480$ (92%)	All Subjects $n = 523$
Age (years) ^a	38 [32–43] (20–65)	39 [35–44] (20–69)	39 [35–44] (20–69)
Years with HIV ^a	6 [2–9] (0–18)	9 [4–13] (0–25)	8 [4–13] (0–25)
Disability ^b			
0	12 (28%)	164 (34%)	176 (34%)
1	14 (33%)	136 (28%)	150 (29%)
2	10 (23%)	100 (21%)	110 (21%)
3	4 (9%)	74 (15%)	78 (15%)
4	3 (7%)	5 (1%)	8 (2%)
5	0	1 (0.2%)	1 (0.2%)
Number that used cannabis to treat symptoms	4/43 (9%)	139/480 (29%)	143/523 (27%)

^aMedian [IQR] (range).

^b0 = none; 1 = mild; 2 = moderate not requiring help from others; 3 = moderate requiring help from others; 4 = severe with almost total loss of function; and 5 = total loss of function.

Table 3
Demographic Differences Between Users and Non-Users of Cannabis for Symptom Control

	Users <i>n</i> = 143	Non-Users <i>n</i> = 380	Statistical Significance
Males:Females	139:4	341:39	<i>P</i> < 0.01
Age ^a	40 [36–44] (26–61)	38 [34–44] (20–69)	<i>P</i> = 0.046
Years with HIV ^a	10 [6–15] (0–25)	7 [3–12] (0–20)	<i>P</i> < 0.01
No disability:Disability	17:126	159:221	<i>P</i> < 0.01

^aMedian [IQR] (range).

before midnight. However, an overlapping group (66/143 [46%]) also reported use at any time if necessary. The reasons for taking the cannabis at these times were reported in a structured format, as detailed in Table 4. A number of reasons related to the time of administration, not least of which was recreational use together with medicinal use. Relief of symptoms of anxiety and depression was common, as was general symptom relief. The reported use for relaxation may reflect the time at which it was taken, namely, during the evening.

Effect on Symptoms

A lack of appetite was the most frequent symptom reported (Table 5) and 97% experienced improvement with cannabis use. Pain was the next most frequent, being present in 45% of patients and improved in 94% of them. The collective results demonstrated statistically significant improvement in half or more patients in symptoms of nausea, anxiety, nerve pain, depression, tingling, numbness, weight loss, headaches, tremor, constipation, and tiredness. Symptoms that were not improved included weakness and slurred speech, and statistically significant memory deterioration was recorded in 47% of users.

Discussion

The demographic characteristics of our cohort of patients (male:female, 11.2:1) is comparable with the UK population of HIV-positive

patients, which has a male:female ratio of 11.5:1. In addition, their ages and duration of HIV disease were comparable with the general UK data for such patients.¹³ Our sample of 523 patients has the highest response rate and is the largest study of its kind. It compares with previous studies, which have had samples ranging from 72 subjects⁷ to 442.⁶ This detailed report of cannabis use for symptom control in a clinically significantly large group of patients can form the basis for more extensive investigations using purified and standardized cannabis extracts.

Despite the fact that cannabis is still illegal, its use for medical purposes appears to be quite widespread. A report from the British Medical Association¹⁴ stated “many normally law abiding citizens—probably many thousands in the developed world” use cannabis illegally for therapy. Wesner¹⁵ reported from an anonymous mail survey of 123 HIV-positive patients in Honolulu that 36.9% of them used cannabis for therapeutic reasons. Approximately one-quarter of 228 HIV-positive men in the Sydney Men and Sexual Health study reported therapeutic use of cannabis.¹⁶ Thirty-two percent (32%) of 72 patients at a clinic in Alabama reported the medical use of marijuana.⁷ These results are comparable to a more recent study carried out in Northern California, in which 33.3% of HIV-positive patients who responded to an anonymous mailed questionnaire used cannabis to treat symptoms associated with their disease.⁶ Our study expanded these findings in a large city clinic population by focusing on the patient’s perceived improvement or worsening of symptoms for which cannabis was considered the origin.

The large number of patients using cannabis as medicinal therapy for symptoms related to HIV raises a number of issues. First, patients are being left with no alternative but to use a non-medical source of supply, which has the

Table 4
Reasons for Using Cannabis

Purpose	<i>n</i>	%
Treat symptoms	77	54
Aid relaxation	121	85
Reduce anxiety	94	66
Relieve depression	75	52
Reduce symptom frequency	29	20
Increase energy levels	15	11
For a ‘high’	62	43

Table 5
Effect of Cannabis on Complaint of Symptoms in 143 HIV Patients

Symptom	Number of Complaints	% Responding					P-value
		Much Better	Little Better	No Change	Little Worse	Much Worse	
Lack of appetite	111	79	18	2	0	1	0.000
Pain in muscles	65	63	31	6	0	0	0.000
Nausea	62	56	37	3	2	2	0.000
Anxiety	98	64	29	3	2	2	0.000
Nerve pain	53	51	40	9	0	0	0.000
Depression	94	56	30	9	4	1	0.000
Tingling	46	37	48	9	7	0	0.000
Numbness	42	36	36	24	5	0	0.000
Weight loss	62	45	24	31	0	0	0.000
Headaches	46	35	30	33	2	0	0.000
Tremor	24	37	29	21	13	0	0.004
Constipation	24	21	29	46	4	0	0.003
Tiredness	60	17	33	33	15	2	0.002
Diarrhea	48	13	23	56	6	2	0.007
Vision dimness	22	9	27	55	9	0	0.109
Weakness	48	10	21	54	15	0	0.134
Memory loss	38	13	5	34	34	13	0.043
Slurred speech	9	11	0	78	11	0	1.00

Note: In ranked order of those demonstrating improvement (recorded as % much better, little better) in comparison to those recorded with no change, little worse, or much worse. The *P*-value in the last column is the exact 2-sided *P*-value for the sign test of no change.

potential for heterogeneity of active cannabinoids, toxic contaminants, inappropriate dose, and drug misuse. Second, if part of the plant material has therapeutic efficacy, the source of this material should be standardized and subjected to clinical trials so that safe and effective use is advocated. Third, the patient is unlikely to divulge cannabis use to their medical team, so that potential drug interactions with prescribed antiretroviral medications may be occurring. In addition, in this study, the number of purely recreational users was not determined so that the overall incidence of drug interactions may be far greater. The type of drug interactions to be considered include loss of cognitive function because it is well-recognized that this is an effect of both cannabis¹⁷ and antiretroviral drugs such as efavirenz.¹⁸ Certainly, the loss of memory reported by these patients is of clinical significance, particularly in the methodological design of clinical trials, and if it is the result of combining preparations, this may be investigated using known standardized cannabinoid therapies. This approach may be one way to reduce additive effects and prevent patients being subject to the effects of unpredictable concentrations of illicit drugs.

The positive responses to symptom control recorded in this study, as exemplified in Table 5, suggest that it is highly probable that cannabinoid medications have a medicinal role in this condition for a number of reasons. First, they

are reported by patients to improve appetite, reduce weight loss, and alleviate nausea.^{19–23} These effects have been recognized and synthetic THC (dronabinol) is licensed for use in the U.S. for this indication. However, no direct comparison has been attempted with a cannabis plant extract that will contain not only THC but also other cannabinoids, of which CBD is reputed to reduce the adverse effects of THC.²⁴ Secondly, pain relief appears to be significant in cannabis users, thereby suggesting a potential target for investigation in the use of cannabinoids as analgesics in HIV patients.

Patients have reported various forms of pain with HIV, such as muscular and neuropathic pain, and these were characterized in the pain maps drawn by the patients. Currently available analgesic drugs have limited efficacy, particularly for neuropathic pain.²⁵ Clearly, there is a need to develop alternative analgesic agents, such as cannabinoids, to improve the choice of therapies. There is animal evidence that cannabinoids have analgesic effects that operate in models of hyperalgesia and allodynia, both indicators of neuropathic pain states,^{26,27} and the discovery of the endogenous cannabinoid system has led scientists to explore the role of endocannabinoids in chronic pain models.^{28,29} However, in clinical practice the choice of natural or synthetic phyto- or endo-cannabinoids for clinical trials is very limited. There have been several anecdotal and clinical trial reports that

cannabis plant extract and synthetic THC and related analogues produce pain relief in humans.³⁰⁻³³ For this present select group of HIV patients, given the reported symptoms experienced using cannabis plant material, there is a strong concern from the medical community managing these patients to limit adverse side effects from self-administered drugs and to provide cannabinoids in a formulation and dosing schedule that avoids harm to the patient. For example, there is strong evidence that the smoking route of administration of cannabis is not safe long-term because of the carcinogenic properties of a cannabis cigarette.³⁴

A pattern of cannabis use emerges from this study that is regular, ongoing, and treats the symptoms of HIV patients to their satisfaction. Given the sedative properties of cannabis, it is important to assess whether evening dosing for cannabinoid therapies is more useful or appropriate. Its sedative effects may be helpful at this time but none were reported as predominant. Presumably there is tolerance to these types of effects.²⁹ More importantly, reduction of pain, anxiety, and gastrointestinal upset appears to be the constellation of symptom control sought by these HIV patients, as shown in Tables 4 and 5.

In relation to HIV, there have been anecdotal reports³⁵ of patients who were already recreational users of cannabis reporting that it improved certain symptoms, such as loss of appetite and nausea, as well as pain and general well being. A small, uncontrolled study of 10 symptomatic AIDS patients reported that dronabinol might be effective in reducing nausea and increasing appetite.¹⁰ Where patients are also medicating with antiretroviral agents, the combination of cannabis and protease inhibitors may be detrimental by altering viral loads. Thus, the effect of smoking on the viral load of HIV-infected patients was investigated by a short-term randomized placebo controlled trial.³⁶ No adverse effects of either therapy were measured with respect to RNA levels, CD4⁺ and CD8⁺ cell counts, or protease inhibitor levels. This brief trial suggests that there are no obvious harmful effects, but these need to be determined using an appropriate route of drug administration and a longer-term study.

There is accumulating evidence that suggests that cannabinoids have therapeutic applications in a variety of neurodegenerative diseases,

such as multiple sclerosis,^{37,38} Huntington's disease,³⁹ and brain injury.⁴⁰ So far, in terms of HIV, the evidence for therapeutic efficacy of cannabinoids is still mainly anecdotal. We have sought to establish if an improvement from cannabis use, albeit self-administered and not standardized, is seen in symptoms such as pain, appetite, and nausea in a large sample of HIV patients. To do this, we expanded on previous research by determining specifically the variety and groups of symptoms that patients select to modify by their use of cannabis. We also secured a therapeutic timetable in order to predict the frequency of drug administration for the patient's selected symptoms. These results will be important in the design of a randomized, placebo-controlled clinical trial comparing conventional treatments to cannabis for symptoms of HIV.

Acknowledgments

The authors thank Dr. Elena Kulinskaya for statistical advice and Dr. Sarah Cox, Dr. Andrew Rice, and the staff at the Kobler Clinic, St. Stephen's Center.

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Appendix **Questionnaire**

HIV Symptoms and the Use of Cannabis

This questionnaire is designed to establish the current use of cannabis for the management of symptoms from HIV in our patients. We would be grateful for some personal details (but not details of identification) and your past and present experiences (if any) with cannabis.

Please complete the following:

General Details:

Sex: MALE/FEMALE (encircle as necessary)

Age:years

Number of years with HIV:

Degree of Disability

Please choose ONE of the following statements which best describes how severely you are affected by the HIV disease, and how it affects your activities of daily living:

- None
- Mild symptoms
- Moderate symptoms—not requiring help from others
- Moderate symptoms—requiring help from others
- Severe symptoms—almost total loss of function
- Total loss of function

Cannabis use

Have you ever used cannabis to relieve your symptoms (as listed below) of HIV? Y/N

If “NO” we thank you for answering this questionnaire and you are not required to complete any more of the questionnaire.

If “YES” please complete the following details:

How do you take the cannabis?

- Smoke Y/N
- Drink Y/N
- Eat Y/N
- Other (state).....

How many years have you used cannabis relieve some of your symptoms?.....years

How many times a day do you use cannabis?.....

How many days a week do you take cannabis?.....

When do you take cannabis: [*Please choose only ONE*]

After 6 pm and before midnight	Y/N
Between 6 am and midday	Y/N
Midday to 6 pm	Y/N
At any time when necessary	Y/N
Just before going to bed	Y/N
At regular intervals during the day	Y/N

Do you take cannabis to: [*You may choose MORE THAN ONE*]

Relieve symptoms	Y/N
Aid relaxation	Y/N
Relieve anxiety	Y/N
Relieve depression	Y/N
Reduce symptom frequency	Y/N
Obtain energy	Y/N
To get a 'high' / Recreational	Y/N

For each symptom in the left-hand column state if the symptom is now present. Then mark for each symptom, whether past or present, its response to cannabis use, i.e., better or worse.

Diagrams are provided below for the question relating to sites of pain, etc.

Symptom (past or present)	Present	Response to cannabis <i>[Please tick ONE box]</i>				
	Y/N	Much better	Little better	Not changed	Little worse	Much worse
Lack of appetite						
Feeling sick, i.e., Nausea						
Anxiety						
Depression						
Tremor						
Headaches						
Weight loss						
Weakness						
Tiredness						
Vision dimness						
Slurred speech						
Tremor						
Memory loss						
Constipation						
Diarrhea						
Muscle pain (please mark on Diagram 1 where you are affected by this)						
Nerve pain (please mark on Diagram 2 where in your body this is)						
Tingling (draw on Diagram 3 where this is)						
Numbness (draw on Diagram 4 where this is)						
Others (please state)						

N.B. Please do not forget to fill in the body diagrams on the next page if you suffer from MUSCLE PAIN, NERVE PAIN, TINGLING OR NUMBNESS.

Once completed please hand over this questionnaire to the reception desk.

THANK YOU.

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

Perm J 2016 Fall;20(4):16-005

E-pub: 10/12/2016

<http://dx.doi.org/10.7812/TPP/16-005>

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.

Acknowledgments

CannaVest Corp, San Diego, CA, which had no involvement in the case study or distribution of the product, provided the CBD oil that was administered to the patient. No financial support was provided.

Kathleen Loudon, ELS, of Loudon Health Communications provided editorial assistance.

How to Cite this Article

Shannon S, Oplia-Lehman J. Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of posttraumatic stress disorder: A case report. *Perm J* 2016 Fall;20(4):16-005. DOI: <http://dx.doi.org/10.7812/TPP/16-005>.

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.

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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.

Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics[†]

Craig Reinerman, Ph.D.*; Helen Nunberg, M.D., M.P.H.**;
Fran Lanthier, M.A.*** & Tom Heddleston, M.A.***

Abstract— Marijuana is a currently illegal psychoactive drug that many physicians believe has substantial therapeutic uses. The medical literature contains a growing number of studies on cannabinoids as well as case studies and anecdotal reports suggesting therapeutic potential. Fifteen states have passed medical marijuana laws, but little is known about the growing population of patients who use marijuana medicinally. This article reports on a sample of 1,746 patients from a network of nine medical marijuana evaluation clinics in California. Patients completed a standardized medical history form; evaluating physicians completed standardized evaluation forms. From this data we describe patient characteristics, self-reported presenting symptoms, physician evaluations, other treatments tried, other drug use, and medical marijuana use practices. Pain, insomnia, and anxiety were the most common conditions for which evaluating physicians recommended medical marijuana. Shifts in the medical marijuana patient population over time, the need for further research, and the issue of diversion are discussed.

Keywords— anxiety, cannabis therapeutics, insomnia, medical marijuana, pain

Medicinal preparations containing marijuana (cannabis) were widely used in many societies for centuries. Dr. William O'Shaughnessy introduced it as a modern medicine in Europe in 1839. Marijuana was

prescribed for therapeutic use in American medical practice for a variety of conditions from the mid-nineteenth century into the twentieth. Marijuana was admitted to the *United States Pharmacopoeia* in 1850 and listed in the *National Formulary* and the *US Dispensatory*. Major pharmaceutical companies including Lilly, Burroughs-Wellcome, and Parke-Davis produced cannabis-based therapeutic agents (Brecher et al. 1972).

[†]The authors thank the medical marijuana patient-applicants for providing the data, the RAND Corporation for funding data collection and data set construction, MediCann for administrative support, the Rosenbaum Foundation for financial support for this research, and Lester Grinspoon and anonymous referees for helpful comments. An earlier version of this article was presented at the 59th Annual Meeting of the Society for the Study of Social Problems, San Francisco, August 9, 2009.

*Professor and Chair, Department of Sociology, University of California, Santa Cruz.

**Private practice, Santa Cruz, CA.

***Instructors and PhD candidates, Department of Sociology, University of California, Santa Cruz.

Please address correspondence and reprint requests to Craig Reinerman, Sociology Department, University of California, Santa Cruz, CA 95064; phone: (831) 459-2617, fax: (831) 459-3518, email: craigr@ucsc.edu

In 1936, the Federal Bureau of Narcotics advocated a law prohibiting its use, which Congress passed in 1937, against the advice of the American Medical Association (Grinspoon & Bakalar 1993:9–11). This law, along with increased prescribing of aspirin and barbiturates, pushed cannabis out of the *United States Pharmacopoeia* and common medical practice by 1942.

After nonmedical cannabis use spread in the 1960s, the number of Americans reporting lifetime prevalence

increased sharply. Recent estimates from the National Survey on Drug Use and Health show that 102,404,000 Americans have used this drug, 41% of the population aged 12 and over, or about half the adult population (SAMHSA 2010). This widespread use led to a gradual rediscovery of the therapeutic uses of cannabis, albeit largely without physician involvement.

Alongside the spread of nonmedical use, in 1964 scientists determined the precise chemical structure of delta-9 tetrahydrocannabinol (THC), thought to be the most significant psychoactive ingredient in cannabis (Gaoni & Mechoulam 1964). This stimulated research in the clinical pharmacology of cannabinoids. Many physicians in clinical practice also recognized the therapeutic potential of cannabis (Irvine 2006; Charuvastra, Freidmann & Stein 2005), specifically, for example, for pain (Woolridge et al. 2005), as an antiemetic for chemotherapy patients (Doblin & Kleiman 1991), or for symptoms of AIDS (Abrams et al. 2003). More recently a broader medical literature documenting the therapeutic properties of endogenous cannabinoids has developed (e.g., Nicoll & Alger 2004; Lehmann et al. 2002; Hall, Degenhart & Currow 2001). Numerous case reports in the medical literature also have suggested that cannabis has therapeutic potential for a variety of conditions. But rigorous experimental research that might determine more precisely the therapeutic efficacy of cannabis for specific conditions has been blocked by the Drug Enforcement Administration (see Zeese 1999; *Alliance for Cannabis Therapeutics v. Drug Enforcement Administration* 1994).

This combination of increasing therapeutic use and federal government opposition ultimately led to passage of new state laws providing for the medical use of cannabis upon physician recommendation. Since 1996, 15 U.S. states and the District of Columbia have passed such laws: California, Alaska, Oregon, Washington, Nevada, Colorado, Maine, Montana, Michigan, and Washington, DC by ballot initiative; Rhode Island, New Mexico, Vermont, Hawaii, and New Jersey by state legislation.

The first of these laws was California's Proposition 215, the Compassionate Use Act, passed in 1996 (*San Francisco Chronicle* 1996). This act made it legal under state law for patients to possess and use cannabis if recommended by their physicians. Numerous medical and scientific associations endorsed medical use of cannabis and/or supported further research into its therapeutic potential. These included the American College of Physicians (2008), the American Public Health Association (1995), the British Medical Association (1997), the Canadian Medical Association (2005), and the Institute of Medicine of the National Academy of Sciences (1999).

Such elections and endorsements notwithstanding, the Bush Administration's Office of National Drug Control Policy threatened to revoke the licenses of physicians who recommended cannabis to patients. One physician

challenged this policy and the U.S. Court of Appeals ruled (in *Conant v. Walters*) in 2002 that it unconstitutionally infringed physicians' First Amendment rights to freedom of speech with their patients (McCarthy 2004). Subsequent legislation and case law have left medical marijuana (MM) patients and their physicians in legal limbo:

- In 2003, the California legislature passed SB 420 to provide specific implementation guidelines for Proposition 215, including how counties should handle MM patient ID cards.
- Most drug law enforcement is done by local police who enforce state, not federal, drug laws. In 2005, The California Attorney General ruled that Proposition 215 is the legitimate will of the voters and is therefore valid under the California Constitution for purposes of state law enforcement. He advised the Highway Patrol and other state law enforcement agencies that under California law MM patients were legally entitled to possess and use cannabis for therapeutic purposes (Hoge 2005).
- In 2006, Bush administration Attorney General Gonzales sought to invalidate state MM laws, and the U.S. Supreme Court ruled (*Gonzales v. Raich* 2006) that the Compassionate Use Act—its legitimate electoral provenance notwithstanding—neither supersedes nor invalidates federal laws that prohibit marijuana use (see Mikos 2009 for a legal analysis of the states' neglected power to legalize behavior that is criminalized under federal law).
- In 2008 the Supreme Court denied without comment an appeal by two California counties that had refused to implement Proposition 215 (*County of San Diego v. San Diego NORML* 2008), thereby letting stand a lower court ruling that upheld SB 420's provisions regarding counties issuing MM identification cards.
- In 2009, Attorney General Eric Holder issued a policy stating that federal drug control agencies would no longer raid MM dispensaries if they operated within state and local laws (Moore 2009).
- That policy notwithstanding, the DEA has continued to raid MM dispensaries in California into 2011 (e.g., Blankstein 2009).

Within this grey area between conflicting state and federal laws, the number of patients who have received recommendations for medical marijuana from physicians has continued to grow, albeit by how much remains unknown. Over 1,000 MM dispensaries, delivery services, and cooperatives are said to be operating in California to meet the demand (NORML 2007). A rough estimate of the number of MM patients in California can be extrapolated from Oregon figures. Unlike California's Compassionate Use Act, Oregon's MM law set up an Oregon Medical Marijuana Program that requires centralized record keeping. As of July, 2009, some 2,983 Oregon-licensed physicians had approved 20,307 applications for MM (Oregon

Department of Human Services 2008). The population of California is 9.7 times that of Oregon (U.S. Census 2007), which yields a crude estimate of 196,978 MM patients in California. This is likely an underestimate because the California statute affords greater latitude to physicians regarding the conditions for which they can recommend MM (“... any other illness for which marijuana provides relief”). Americans for Safe Access (2008), a MM patient advocacy group, has estimated that there are well over 200,000 physician-sanctioned MM patients in California.

Despite their growing numbers, however, the ambiguous legal status of MM patients renders them a half-hidden population whose characteristics are not well documented, with the partial exception of the San Francisco Bay Area (O’Connell & Bou-Matar 2007; Reiman 2007a). Medical marijuana will likely continue to be a contentious issue, but across fifteen states and the District of Columbia several hundred thousand people are using marijuana as a medicine recommended by physicians, and yet little is known about them as a patient population.

We intend this study as a modest contribution toward filling this gap. It presents data on the demographic characteristics, presenting symptoms, physician evaluations, conventional treatments tried, and MM use practices of patients from a network of MM assessment clinics in California.

METHODS

These data were drawn from 1,746 consecutive admissions to nine MM assessment clinics operating in California in July, August, and September 2006. These assessment clinics are not dispensaries and are not connected to dispensaries. They were located throughout the state—in the north and south, coast and central valley, and large and small cities: Modesto, Oakland, Sacramento, Hollywood, San Diego, Santa Cruz, Ukiah, San Francisco, and Santa Rosa. They charged \$100 to \$125 for an assessment. At the time our sample was drawn, these assessment clinics had evaluated over 54,000 MM patients. Without a comprehensive patient database or representative household surveys, there is no way to determine precisely how representative this sample is of the overall population of MM patients. Moreover, there is a large albeit unknown number of people who use marijuana medicinally but who have not sought physician recommendations or official patient ID cards, perhaps because of the expense of the assessment.¹

Evaluating physicians interviewed potential patients and evaluated their patient medical histories for purposes of recommending MM and issuing patient identification cards under the Compassionate Use Act and SB 420. The evaluation instruments were (1) a basic patient-administered medical history questionnaire covering demographics, presenting symptoms or conditions, brief medical history,

conventional and alternative medical treatments tried, drug use history, and MM use practices; and (2) a physician evaluation form using International Classification of Diseases codes (ICD-9). Each patient received and signed an extensive informed consent form noting confidentiality, which was approved by the clinics’ IRB.

Most prior studies of MM patients are based on small, symptom-specific samples. Initially, the population of MM patients in the San Francisco Bay Area were people with HIV/AIDS and cancer (e.g., Harris, Mendelson & Jones 1998). Later, physicians began to recommend cannabis to patients with chronic pain, mood disorders and other psychiatric conditions (Gieringer 2002). The data reported here describe what is among the largest and most symptomatically and demographically diverse samples of medical cannabis patients to date (cf., O’Connell & Bou-Matar 2007).

RESULTS

As Table 1 indicates, the MM patients are three-fourths male and three-fifths White. Compared to the US Census of California, the patients in this sample are on average somewhat younger, report slightly more years of formal education, and are more often employed. The comparison also indicates that women, Latinos, and Asian Americans are underrepresented. Given the limitations of our data, we can offer only informed speculation as to why.

The underrepresentation of women may be in part an epidemiological artifact of the gender distribution of certain kinds of injuries (e.g., workplace, sports, and motorcycle accidents). It may also have to do with the double stigma women face in seeking MM—for using an illicit drug and for violating gender-specific norms against illegal behavior in general. Moreover, as with alcohol use, pregnant women and women considering pregnancy are likely to have health concerns and many may fear that MM could put them in jeopardy if discovered by child protection agencies.

Given the high poverty rate among Latinos and their concentration in the manual labor end of the occupational structure, Latinos are exposed to equal or greater risks of work-related injuries and to no less epidemiologic risk of other conditions for which MM is sometimes used. It seems likely that their under-representation has to do with the undocumented status of many Latinos in California. The undocumented often avoid contact with government agencies for fear of apprehension by law enforcement, for beyond arrest and incarceration this carries the risk of deportation. Such fears reduce the likelihood of Latinos accessing health care in general and MM in particular. Asian Americans are also underrepresented, but this may be because they have lower prevalence of marijuana use than other racial/ethnic groups and/or because they have their own venerable traditions of herbal medicine.

TABLE 1
Demographic Characteristics of California Medical Marijuana Patients Compared to California Census 2000, Age 18 and Over (n = 1746)

	MM Patients	U.S. Census 2000 – California
Female	27.1%	50.7%
Male	72.9%	49.3%
White	61.5%	59.5%
Latino	14.4%	32.4%
African American	11.8%	6.7%
Native American	4.5%	1.0%
Asian/Pacific Islander	4.2%	11.2%
Other	4.3%	*
18–24 Years Old	17.9%	~17.1%
25–34 "	27.5%	15.4%
35–44 "	21.3%	16.2%
45–54 "	20.4%	12.8%
55> "	12.6%	18.4%
<High School	8.8%	*
High School Graduate	42.2%	*
Some College	27.1%	*
College Graduate>	23.8%	*
Employed	64.8%	57.5%
Health Insurance	73.4%	*

*Data not available in California Census.

African-Americans, conversely, are over-represented in this sample. This does not appear to stem from their prevalence of marijuana use, for representative national surveys show that Blacks generally do not have significantly higher prevalence of marijuana use than Whites (SAMHSA 2005). African-Americans may be more likely to seek MM for any of several reasons: because they are disproportionately poor, more often lack health insurance, are significantly less likely to be prescribed other medication for pain (Pletcher et al. 2008) or to receive treatment for cancer (Gross et al. 2008), and because African-Americans are a growing proportion of HIV/AIDS cases. Some of these same reasons may help to explain why Native Americans are also overrepresented, although their proportion of both this sample and the general population is too small to judge representativeness accurately.

In their medical history questionnaires, patients were asked "Which of the following best describe the therapeutic benefit you receive from medicinal cannabis? (Check the most important)." Patients typically reported more than one therapeutic benefit (mean = 3). Early studies showed most patients used MM to relieve symptoms of HIV/AIDS (Woolridge et al. 2005) or cancer, and it is likely that the majority of patients in our sample who reported "nausea" were cancer patients receiving chemotherapy. However, Table 2 suggests that cancer and AIDS patients are now a

TABLE 2
Patient Self-Reports of Therapeutic Benefits from Medicinal Marijuana*

	Percent
To Relieve:	
Pain	82.6
Muscle Spasms	41.1
Headaches	40.7
Anxiety	37.8
Nausea/Vomiting	27.7
Depression	26.1
Cramps	19.0
Panic Attacks	16.9
Diarrhea	5.0
Itching	2.8
To Improve:	
Sleep	70.7
Relaxation	55.1
Appetite	37.7
Concentration/Focus	22.9
Energy	15.9
To Prevent:	
Medication Side Effects	22.5
Anger	22.4
Involuntary Movements	6.2
Seizures	3.2
As Substitute for:	
Prescription Medication	50.9
Alcohol	13.0

*N = 1,745; patients could report more than one benefit in more than one category.

significantly smaller proportion of the total (e.g., "to relieve nausea/vomiting" 27.7%, "to improve appetite" 37.7%) and that the MM patient population has become more diverse since the Compassionate Use Act was passed in 1996 (cf. Ware, Adams & Guy 2005, on MM use in the UK, and Grotenherman 2002 on MM use in Germany).

Instead, relief of pain, muscle spasms, headache, and anxiety, as well as to improve sleep and relaxation were the most common reasons patients cited for using MM. Chronic pain also topped the list of maladies for which MM was used in another California clinical sample (Reiman 2007b).

Table 3 shows the ICD-9 diagnostic codes most frequently recorded by evaluating physicians. Pain from back and neck injuries was the most frequently coded. This appears consistent with a nationally representative Medical Expenditure Panel Survey, which found a 19.3% increase in the prevalence of spine problems between 1997 and 2005 (Martin et al. 2008). Back and neck pain was followed in frequency by sleep disorders (also increasing), anxiety/depression, muscle spasms, and arthritis. Fully half of this sample reported using MM as a substitute

TABLE 3
Conditions Most Frequently Recorded by Physicians As Reasons for Approving Medical Marijuana Patient Identification Cards*

	Percent	ICD-9 Codes
Back/Spine/Neck Pain	30.6%	[722.1–724.2]
Sleep Disorders	15.7%	[307.42, 327.0]
Anxiety/Depression	13.0%	[300.0, 311.0]
Muscle Spasms	9.5%	[728.85]
Arthritis	8.5%	[715.0, 721.2, 721.2]
Injuries (Knee, Ankle, Foot)	4.5%	[959.7]
Joint Disease/Disorders	4.4%	[716.1–719.49]
Narcolepsy	3.7%	[347.0]
Nausea	3.4%	[787.02]
Inflammation (Spine, Nerve)	2.9%	[724.4]
Headaches/Migraines	2.7%	[784.0, 346.0, 346.2]
Eating Disorders	1.1%	[783.0]

*N = 1746; some patients reported multiple symptoms and/or conditions.

TABLE 4
Other Treatment Modalities Tried for the Medical Condition(s) for Which Patients Seek Medical Marijuana*

	%	N
Prescription Medication	79.3%	1383
Physical Therapy	48.7	850
Chiropractic	36.3	633
Surgery	22.3	389
Counseling	21.0	366
Acupuncture	19.4	338
Therapeutic Injection	15.4	269
Homeopathy	12.0	209
Other Types of Treatment	11.9	208

*N = 1746; patients could report multiple other treatments.

for prescription drugs, consistent with other studies (e.g., Reiman 2007a).

Table 4 indicates that the MM patients in the sample had tried a variety of other treatments, conventional and alternative, for the conditions for which they were seeking a MM identification card. Four in five (79.3%) reported having tried other medications prescribed by their physicians (almost half were opiates); about half (48.7%) had tried physical therapy; over a third (36.3%) had tried chiropractic; nearly one-fourth (22.3%) reported having had surgery for their condition.

Table 5 compares patient responses to the drug use questions to those in the 2006 National Survey on Drug Use and Health (SAMHSA 2007). Prevalence of tobacco

TABLE 5
Medical Marijuana Patients' Self-Reported Current Nonmedical Drug Use, Compared to 2006 National Survey on Drug Use And Health (SAMHSA 2007)

	MM Patients	NSDUH*
Tobacco	29.4%	25.0%
Alcohol	47.5	61.9
Cocaine	0.3	1.9
Methamphetamine	0.4	0.5
Heroin	0.1	0.3
Other Opiates	1.2	**

Note: Participants were asked "Do you currently use . . ."; answers are percent responding "yes." N = 1745; patients could report more than one drug. Of smokers, 65.5% used ten or less cigarettes/day; of drinkers, 58.7% used \leq one or less drinks/day.

*NSDUH figures for "past month" prevalence used as a proxy for "current use".

**Data not available in comparable form.

use was somewhat higher than in the general population, but prevalence of alcohol use was significantly lower. Many patients reported that they valued MM because it allowed them to reduce their alcohol use. It is possible that self-reports on a self-administered instrument will underestimate illicit drug use, particularly if patients felt that admitting illicit drug use could reduce their chances of obtaining a MM identification card. Rigorous assessments of the reliability of such data must await further research, but limitations aside, these data suggest low prevalence of other illicit drug use among MM patients. While it is true that the great majority of our respondents had used marijuana recreationally, in response to a separate question over two-fifths (41.2%) reported that they had *not* been using it recreationally prior to trying it for medicinal purposes.

Table 6 presents data on patients' medical marijuana use practices. Amounts used per week varied from three grams or less (40.1%) to seven or more grams (23.3%). Two-thirds (67%) reported using MM daily while one-fourth (26%) reported using less than once a week. Half (52.9%) reported using one or two times per day while one in ten (10%) reported using three or more times per day. Patients consumed MM primarily in the evenings (52.3%) or prior to sleep (56.1%). More than two in five (42.3%) reported that when they used depended on their medical symptoms. Patients ingested MM predominantly by smoking (86.1%), although one-fourth (24.4%) reported ingesting orally and nearly a fourth (21.8%) reported using a vaporizer. These latter figures suggest that at least some of the time, many MM patients are choosing modes of ingestion that reduce the perceived risk of harms from smoking (Tan et al. 2009; Hashibe et al. 2006).

TABLE 6
Medical Marijuana Use Practices

Frequency of Medical Marijuana Use (N = 1583)*	
Daily	67.0% (1065)
<Once A Week	26.0% (409)
<Once A Month	7.0% (109)
On Days Used, Frequency per Day (N = 1574)	
1 To 2 Times Per Day	52.9% (833)
2 To 3 Times Per Day	29.0% (457)
>3 Times Per Day	10.0% (284)
Time Of Day Typically Used (N = 1745)	
Prior To Sleep	56.1% (979)
Evenings	52.3% (913)
Depends on Symptoms	42.3% (739)
Mornings	25.7% (448)
Afternoons	20.1% (350)
After Work	12.4% (217)
Middle of the Night	6.5% (114)
All Day	5.3% (93)
Mode of Ingestion (N = 1745)	
Smoke	86.1% (1503)
Oral Ingestion	24.4% (426)
Vapor	21.8% (380)
Topical	2.8% (49)
Amount Used per Week (N = 1431)	
0–3 Grams	40.1% (574)
4–7 Grams	36.5% (523)
>7 Grams	23.3% (334)

*Total n = 1745, but N's vary across questions because patients could choose more than one response and because not all responded to each question.

DISCUSSION

Rediscovery of Medicinal Utility and Diversifying Patient Population

Compared to earlier studies of MM patients, these data suggest that the patient population has evolved from mostly HIV/AIDS and cancer patients to a significantly more diverse array. The diffusion of marijuana as a medicine may have been slower than that of other medicines in conventional clinical practice because the flow of information from physician to patient is impeded by MM's ambiguous legal status. Thus, information about the potential therapeutic utility of cannabis is spread mostly via word of mouth and other informal means. This suggests that the patient population is likely to continue evolving as new patients and physicians discover the therapeutic uses of cannabis. Ironically, this trend toward increasing therapeutic uses is bringing marijuana back to the position it held in the U.S. Pharmacopeia prior to its prohibition in 1937.

Further Research

Like other medicines, marijuana's therapeutic efficacy varies across conditions and patient groups. This variation seems more likely when supplies remain illicit because standardized dosages or other quality controls are more difficult to achieve. To gain maximum therapeutic potential across the growing range of conditions for which MM is being recommended, more systematic research is needed. Longitudinal, case control, and double-blind studies are required to rigorously assess marijuana's therapeutic efficacy for specific patient groups, conditions, and diseases. With regard to shifts in the patient population, it also would be very useful to have follow-up studies of patients accessing the assessment clinics in our sample and others drawn from similar assessment clinics.

Diversion

Critics have argued that some MM patients are "gaming the system" to get marijuana for nonmedical use. Neither our data nor any other data we are aware of allow any clear-cut, empirical estimate of the scale of such diversion. Given the widespread nonmedical use marijuana in the general population (102,404,000 Americans report lifetime prevalence; see SAMHSA 2010) and the risk of arrest (847,864 Americans were arrested for marijuana offenses in 2008, 754,224 or 88.96% of them for possession alone; FBI 2009), it seems likely that at least some MM patients use MM dispensaries as sources of supply for nonmedical use.

Defining and measuring such diversion, however, is complicated at best. Given the high prevalence of nonmedical use, it is not surprising that most MM patients in our sample reported having used it recreationally before using it therapeutically. But as noted above, two-fifths had *not* been using marijuana recreationally prior to trying it for medicinal purposes. Their self-reported rates of other illicit drug use are slightly lower than those found among the general population, and their levels of educational attainment and rate of employment are comparable to the California population. Our data have clear limitations, but they contain no obvious signs that MM patients differ from the general population.

Nor is drug diversion unique to medical marijuana. A significant albeit unknown proportion of other patients obtain prescriptions for numerous drugs through legal medical channels that they then use for nonmedical purposes, for example, Valium and other benzodiazepines (Haafkens 1997), Ritalin and other stimulants prescribed for ADHD, and Oxycontin and other opiates prescribed for pain.

The diversion issue will likely become more important as the line between medical and nonmedical drug use is increasingly blurred (Murray, Gaylin & Macklin 1984). Beyond the spread of MM, Prozac and other SSRI-type antidepressants, for example, are often prescribed

for patients who do not meet DSM criteria for clinical depression but who simply feel better when taking it. Such “cosmetic psychopharmacology” (Kramer 1993) is likely to grow as new psychiatric medications come to market. The line between medical and nonmedical drug use has also been blurred by performance enhancing drugs such as steroids, so-called “smart drugs” that combine vitamins with psychoactive ingredients, and herbal remedies like *ma huang* (ephedra) available in health food stores (Burros & Jay 1996).

These examples suggest that despite the best intentions of physicians and law makers, much drug use does not fit into two neat boxes, medical and nonmedical, but rather exists on a continuum where one shades into the other as

patients’ purposes shift to suit situational exigencies in their health and their daily lives. It is not clear where a border line between medical and nonmedical marijuana or other drug use might be drawn nor how it might be effectively policed (see Reinarman & Levine 1997: 334–44).

NOTE

1. We are grateful to one anonymous reviewer for pointing out that the cost of these assessments may well have prevented some potential MM patients—including many impoverished HIV/AIDS patients—from obtaining ID cards, which may have affected the demographics of this sample.

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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

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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: drtroutt@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.

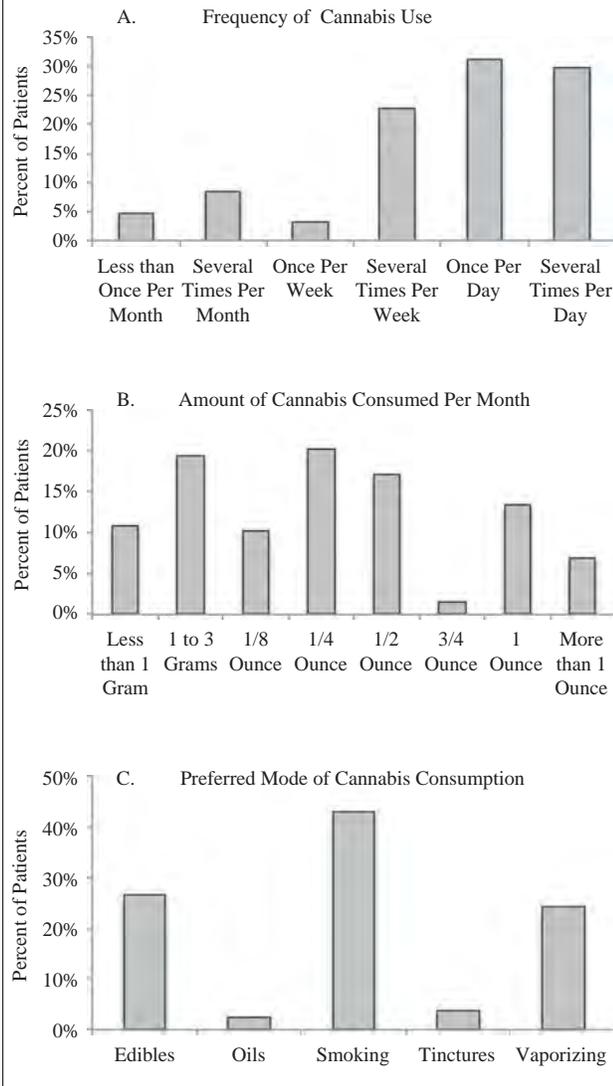
Perceived Effects of Medical Cannabis Legalization

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

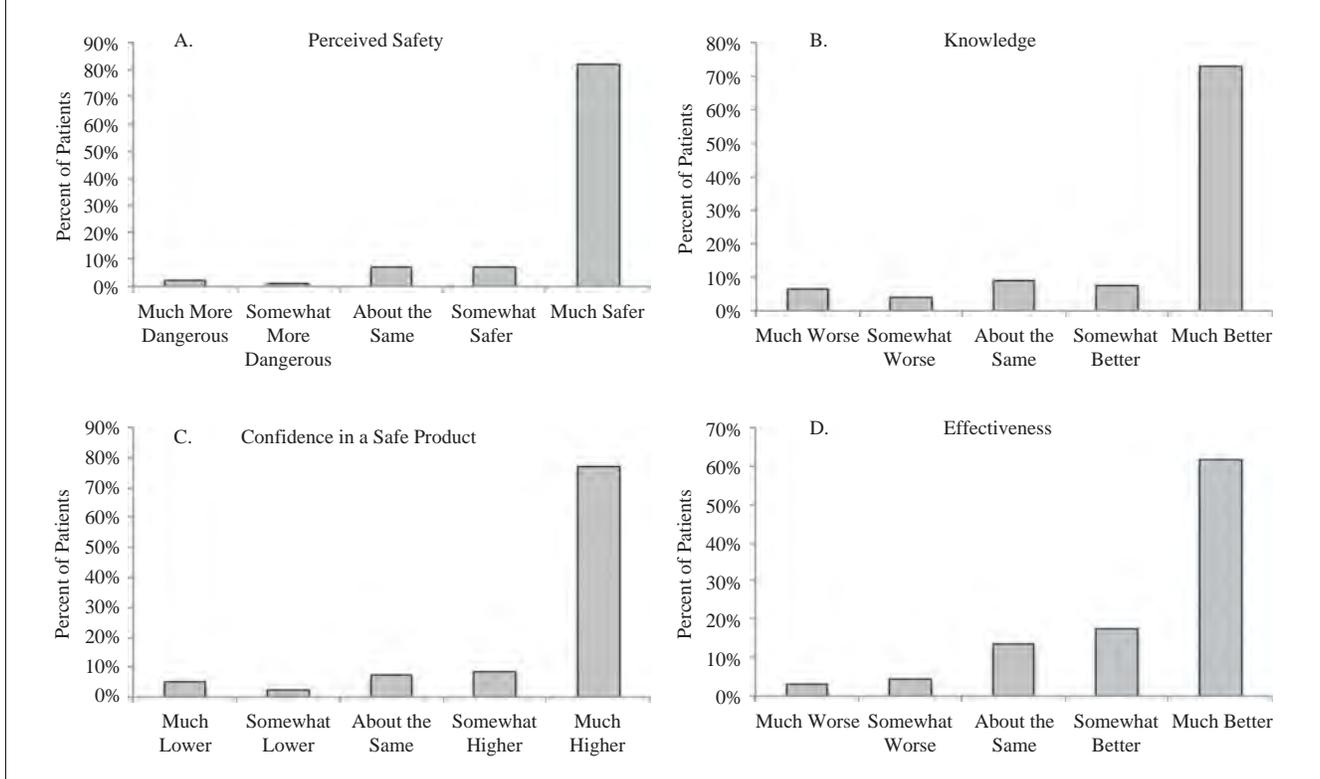
Consistent with research in other states (Bonn-Miller et al. 2014; Aggarwal et al. 2013; Ilgen et al. 2013; Nunberg et al. 2011; Reinerman et al. 2011; Aggarwal et al. 2009; Reiman 2009; O’Connell and Bou-Matar 2007; Harris et al. 2000), participants in the present study were mostly White men. Average 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

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

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.

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REVIEW

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

Ethan B Russo

GW Pharmaceuticals, Salisbury, Wiltshire, UK

Correspondence

Ethan Russo, MD, 20402 81st
Avenue SW, Vashon, WA 98070,
USA. E-mail:
ethanrusso@comcast.net

Keywords

cannabinoids; terpenoids;
essential oils; THC; CBD;
limonene; pinene; linalool;
caryophyllene; phytotherapy

Received

19 November 2010

Revised

29 December 2010

Accepted

12 January 2011

Tetrahydrocannabinol (THC) has been the primary focus of cannabis research since 1964, when Raphael Mechoulam isolated and synthesized it. More recently, the synergistic contributions of cannabidiol to cannabis pharmacology and analgesia have been scientifically demonstrated. Other phytocannabinoids, including tetrahydrocannabivarin, cannabigerol and cannabichromene, exert additional effects of therapeutic interest. Innovative conventional plant breeding has yielded cannabis chemotypes expressing high titres of each component for future study. This review will explore another echelon of phytotherapeutic agents, the cannabis terpenoids: limonene, myrcene, α -pinene, linalool, β -caryophyllene, caryophyllene oxide, nerolidol and phytol. Terpenoids share a precursor with phytocannabinoids, and are all flavour and fragrance components common to human diets that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies. Terpenoids are quite potent, and affect animal and even human behaviour when inhaled from ambient air at serum levels in the single digits $\text{ng}\cdot\text{mL}^{-1}$. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. Particular focus will be placed on phytocannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant *Staphylococcus aureus*). Scientific evidence is presented for non-cannabinoid plant components as putative antidotes to intoxicating effects of THC that could increase its therapeutic index. Methods for investigating entourage effects in future experiments will be proposed. Phytocannabinoid-terpenoid synergy, if proven, increases the likelihood that an extensive pipeline of new therapeutic products is possible from this venerable plant.

LINKED ARTICLES

This article is part of a themed issue on Cannabinoids in Biology and Medicine. To view the other articles in this issue visit <http://dx.doi.org/10.1111/bph.2011.163.issue-7>

Abbreviations

2-AG, 2-arachidonoylglycerol; 5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; AEA, arachidonylethanolamide (anandamide); AI, anti-inflammatory; AMPA, α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; Ca^{++} , calcium ion; CB_1/CB_2 , cannabinoid receptor 1 or 2; CBC, cannabichromene; CBCA, cannabichromenic acid; CBD, cannabidiol; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBG, cannabigerol; CBGA, cannabigerolic acid; CBGV, cannabigerivarin; CNS, central nervous system; COX, cyclo-oxygenase; DAGL, diacylglycerol lipase; ECS, endocannabinoid system; EO, essential oil; FAAH, fatty acid amidohydrolase; FDA, US Food and Drug Administration; FEMA, Food and Extract Manufacturers Association; fMRI, functional magnetic resonance imaging; GABA, gamma aminobutyric acid; GPCR, G-protein coupled receptor; GPR, G-protein coupled receptor; HEK, human embryonic kidney; IC_{50} , 50% inhibitory concentration; i.p., intraperitoneal; MAGL, monoacylglycerol lipase; MIC, minimum inhibitory concentration; MS, multiple sclerosis; NGF, nerve growth factor; NIDA, US National Institute on Drug Abuse; PG, prostaglandin; PTSD, post-traumatic stress disorder; RCT, randomized clinical trial; SPECT, single photon emission computed tomography; SSADH, succinic semialdehyde dehydrogenase; Sx, symptoms; $T_{1/2}$, half-life; TCA, tricyclic antidepressant; THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; THCV, tetrahydrocannabivarin; $\text{TNF-}\alpha$, tumour necrosis factor-alpha, TRPV, transient receptor potential vanilloid receptor

The roots of cannabis synergy

Cannabis has been a medicinal plant of unparalleled versatility for millennia (Mechoulam, 1986; Russo, 2007; 2008), but whose mechanisms of action were an unsolved mystery until the discovery of tetrahydrocannabinol (THC) (Gaoni and Mechoulam, 1964a), the first cannabinoid receptor, CB₁ (Devane *et al.*, 1988), and the endocannabinoids, anandamide (arachidonylethanolamide, AEA) (Devane *et al.*, 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995). While a host of phytocannabinoids were discovered in the 1960s: cannabidiol (CBD) (Mechoulam and Shvo, 1963), cannabigerol (CBG) (Gaoni and Mechoulam, 1964b), cannabichromene (CBC) (Gaoni and Mechoulam, 1966), cannabidivarin (CBDV) (Vollner *et al.*, 1969) and tetrahydrocannabivarin (THCV) (Gill *et al.*, 1970), the overwhelming preponderance of research focused on psychoactive THC. Only recently has renewed interest been manifest in THC analogues, while other key components of the activity of cannabis and its extracts, the cannabis terpenoids, remain understudied (McPartland and Russo, 2001b; Russo and McPartland, 2003). The current review will reconsider essential oil (EO) agents, their peculiar pharmacology and possible therapeutic interactions with phytocannabinoids. Nomenclature follows conventions in Alexander *et al.* (2009).

Phytocannabinoids and terpenoids are synthesized in cannabis, in secretory cells inside glandular trichomes (Figure 1) that are most highly concentrated in unfertilized female flowers prior to senescence (Potter, 2004; Potter, 2009). Geranyl pyrophosphate is formed as a precursor via the deoxyxylulose pathway in cannabis (Fellermeier *et al.*, 2001), and is a parent compound to both phytocannabinoids and terpenoids (Figure 2). After coupling with either olivetolic acid or divarinic acid, pentyl or propyl cannabinoid acids are produced, respectively, via enzymes that accept either substrate (de Meijer *et al.*, 2003), a manifestation of Mechoulam's postulated 'Nature's Law of Stinginess'. Although having important biochemical properties in their own right, acid forms of phytocannabinoids are most commonly decarboxylated via heat to produce the more familiar neutral phytocannabinoids (Table 1). Alternatively, geranyl



Figure 1

Cannabis capitate glandular (EBR by permission of Bedrocan BV, Netherlands).

pyrophosphate may form limonene and other monoterpenoids in secretory cell plastids, or couple with isopentenyl pyrophosphate in the cytoplasm to form farnesyl pyrophosphate, parent compound to the sesquiterpenoids, that co-localizes with transient receptor potential vanilloid receptor (TRPV) 1 in human dorsal root ganglion, suggesting a role in sensory processing of noxious stimuli (Bradshaw *et al.*, 2009), and which is the most potent endogenous ligand to date on the G-protein coupled receptor (GPR) 92 (Oh *et al.*, 2008).

An obvious question pertains to the chemical ecology of such syntheses that require obvious metabolic demands on the plant (Gershenzon, 1994), and these will be considered.

Is cannabis merely a crude vehicle for delivery of THC? Might it rather display herbal synergy (Williamson, 2001) encompassing potentiation of activity by active or inactive components, antagonism (evidenced by the ability of CBD to reduce side effects of THC; Russo and Guy, 2006), summation, pharmacokinetic and metabolic interactions? Recently, four basic mechanisms of synergy have been proposed (Wagner and Ulrich-Merzenich, 2009): (i) multi-target effects; (ii) pharmacokinetic effects such as improved solubility or bioavailability; (iii) agent interactions affecting bacterial resistance; and (iv) modulation of adverse events. Cannabis was cited as an illustration.

Could phytocannabinoids function analogously to the endocannabinoid system (ECS) with its combination of active and 'inactive' synergists, first described as an entourage (Ben-Shabat *et al.*, 1998), with subsequent refinement (Mechoulam and Ben-Shabat, 1999) and qualification (p. 136): 'This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them'. Support derives from studies in which cannabis extracts demonstrated effects two to four times greater than THC (Carlini *et al.*, 1974); unidentified THC antagonists and synergists were claimed (Fairbairn and Pickens, 1981), anti-convulsant activity was observed beyond the cannabinoid fraction (Wilkinson *et al.*, 2003), and extracts of THC and CBD modulated effects in hippocampal neurones distinctly from pure compounds (Ryan *et al.*, 2006). Older literature also presented refutations: no observed differences were noted by humans ingesting or smoking pure THC versus herbal cannabis (Wachtel *et al.*, 2002); pure THC seemed to account for all tetrad-type effects in mice (Varvel *et al.*, 2005); and smoked cannabis with varying CBD or CBC content failed to yield subjective differences combined with THC (Ilan *et al.*, 2005). Explanations include that the cannabis employed by Wachtel yielded 2.11% THC, but with only 0.3% cannabinol (CBN) and 0.05% CBD (Russo and McPartland, 2003), and Ilan's admission that CBN and CBD content might be too low to modulate THC. Another factor is apparent in that terpenoid yields from vaporization of street cannabis were 4.3–8.5 times of those from US National Institute on Drug Abuse cannabis (Bloor *et al.*, 2008). It is undisputed that the black market cannabis in the UK (Potter *et al.*, 2008), Continental Europe (King *et al.*, 2005) and the USA (Mehmedic *et al.*, 2010) has become almost exclusively a high-THC preparation to the almost total exclusion of other phytocannabinoids. If – as many consumers and experts maintain (Clarke, 2010) – there are biochemical, pharmacological and

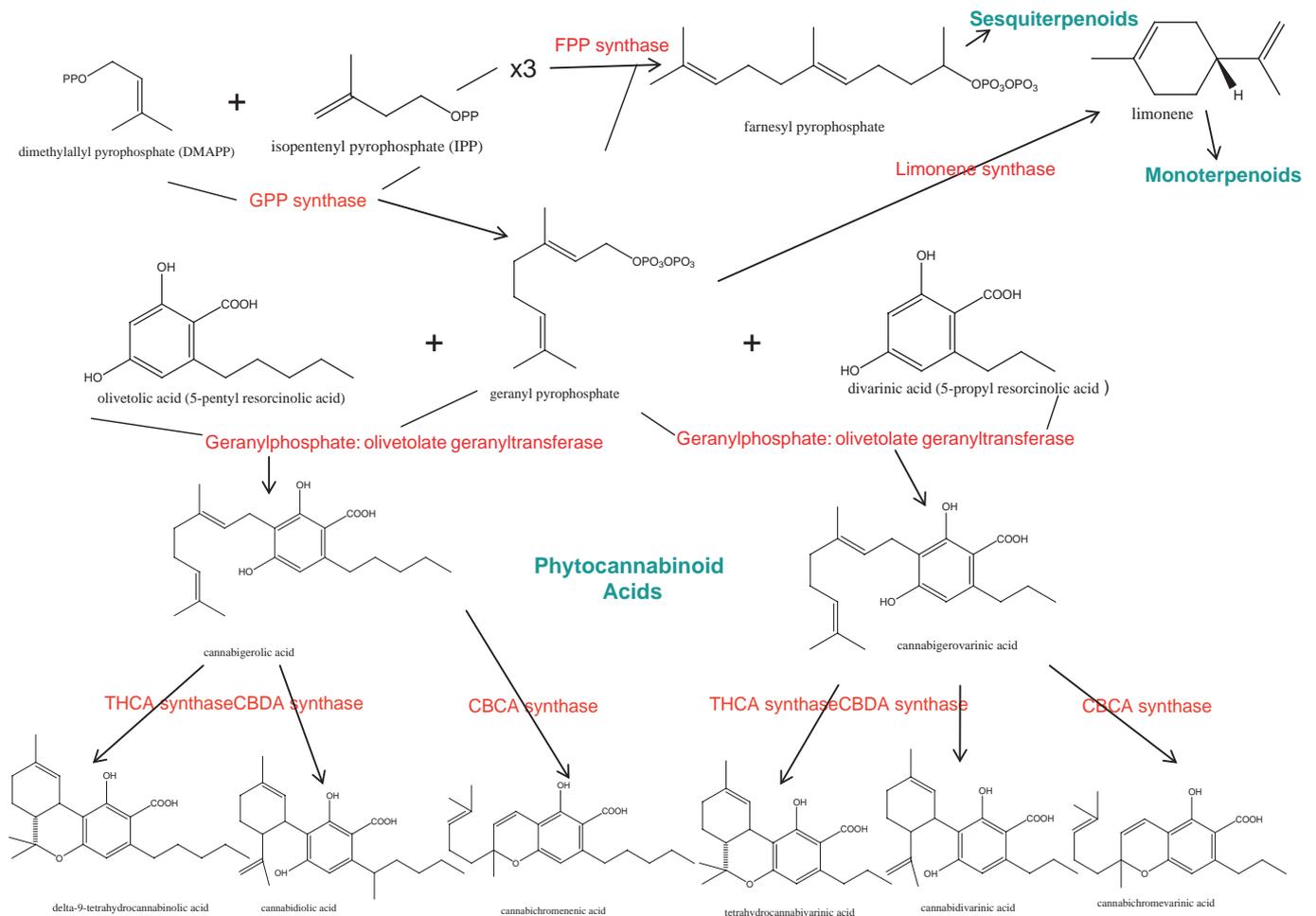


Figure 2
Phytocannabinoid and cannabis terpenoid biosynthesis.

phenomenological distinctions between available cannabis ‘strains’, such phenomena are most likely related to relative terpenoid contents and ratios. This treatise will assess additional evidence for putative synergistic phytocannabinoid-terpenoid effects exclusive of THC, to ascertain whether this botanical may fulfil its promise as, ‘a neglected pharmacological treasure trove’ (Mechoulam, 2005).

Phytocannabinoids, beyond THC: a brief survey

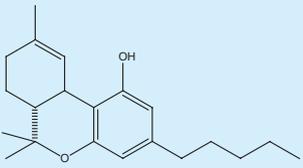
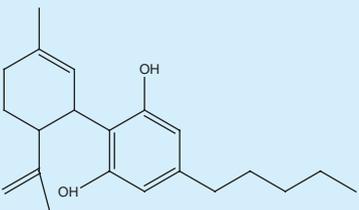
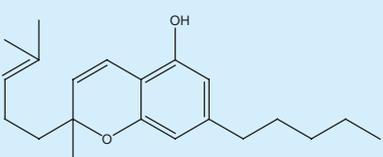
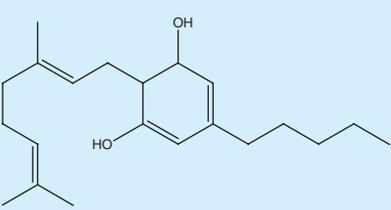
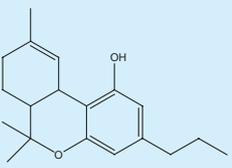
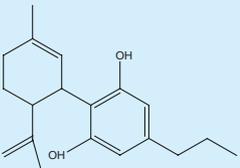
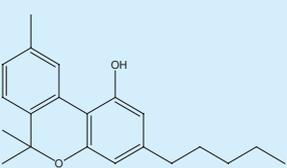
Phytocannabinoids are exclusively produced in cannabis (*vide infra* for exception), but their evolutionary and ecological *raison d’être* were obscure until recently. THC production is maximized with increased light energy (Potter, 2009). It has been known for some time that CBG and CBC are mildly antifungal (ElSohly *et al.*, 1982), as are THC and CBD against a cannabis pathogen (McPartland, 1984). More pertinent, however, is the mechanical stickiness of the trichomes, capable of trapping insects with all six legs

(Potter, 2009). Tetrahydrocannabinolic acid (THCA) and cannabichromenic acid (Morimoto *et al.*, 2007), as well as cannabidiolic acid and cannabigerolic acid (CBGA; Shoyama *et al.*, 2008) produce necrosis in plant cells. Normally, the cannabinoid acids are sequestered in trichomes away from the flower tissues. Any trichome breakage at senescence may contribute to natural pruning of lower fan leaves that otherwise utilize energy that the plant preferentially diverts to the flower, in continued efforts to affect fertilization, generally in vain when subject to human horticulture for pharmaceutical production. THCA and CBGA have also proven to be insecticidal in their own right (Sirikantaramas *et al.*, 2005).

Over 100 phytocannabinoids have been identified (Brenneisen, 2007; Mehmedic *et al.*, 2010), but many are artefacts of analysis or are produced in trace quantities that have not permitted thorough investigation. The pharmacology of the more accessible phytocannabinoids has received excellent recent reviews (Pertwee *et al.*, 2007; Izzo *et al.*, 2009; De Petrocellis and Di Marzo, 2010; De Petrocellis *et al.*, 2011), and will be summarized here, with emphasis on activities with particular synergistic potential.

Table 1

Phytocannabinoid activity table

Phytocannabinoid structure	Selected pharmacology (reference)	Synergistic terpenoids
 <p>delta-9-tetrahydrocannabinol (THC)</p>	<p>Analgesic via CB₁ and CB₂ (Rahn and Hohmann, 2009) AI/antioxidant (Hampson <i>et al.</i>, 1998) Bronchodilatory (Williams <i>et al.</i>, 1976) ↓ Sx. Alzheimer disease (Volicer <i>et al.</i>, 1997; Eubanks <i>et al.</i>, 2006) Benefit on duodenal ulcers (Douthwaite, 1947) Muscle relaxant (Kavia <i>et al.</i>, 2010) Antipruritic, cholestatic jaundice (Neff <i>et al.</i>, 2002)</p>	<p>Various Limonene <i>et al.</i> Pinene Limonene, pinene, linalool Caryophyllene, limonene Linalool? Caryophyllene?</p>
 <p>cannabidiol</p>	<p>AI/antioxidant (Hampson <i>et al.</i>, 1998) Anti-anxiety via 5-HT_{1A} (Russo <i>et al.</i>, 2005) Anticonvulsant (Jones <i>et al.</i>, 2010) Cytotoxic versus breast cancer (Ligresti <i>et al.</i>, 2006) ↑ adenosine A_{2A} signalling (Carrier <i>et al.</i>, 2006) Effective versus MRSA (Appendino <i>et al.</i>, 2008) Decreases sebum/sebocytes (Biro <i>et al.</i>, 2009) Treatment of addiction (see text)</p>	<p>Limonene <i>et al.</i> Linalool, limonene Linalool Limonene Linalool Pinene Pinene, limonene, linalool Caryophyllene</p>
 <p>cannabichromene</p>	<p>Anti-inflammatory/analgesic (Davis and Hatoum, 1983) Antifungal (EISOHly <i>et al.</i>, 1982) AEA uptake inhibitor (De Petrocellis <i>et al.</i>, 2011) Antidepressant in rodent model (Deyo and Musty, 2003)</p>	<p>Various Caryophyllene oxide – Limonene</p>
 <p>cannabigerol</p>	<p>TRPM8 antagonist prostate cancer (De Petrocellis <i>et al.</i>, 2011) GABA uptake inhibitor (Banerjee <i>et al.</i>, 1975) Anti-fungal (EISOHly <i>et al.</i>, 1982) Antidepressant rodent model (Musty and Deyo, 2006); and via 5-HT_{1A} antagonism (Cascio <i>et al.</i>, 2010) Analgesic, α-2 adrenergic blockade (Cascio <i>et al.</i>, 2010) ↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007) Effective versus MRSA (Appendino <i>et al.</i>, 2008)</p>	<p>Various Cannabis terpenoids Phytol, linalool Caryophyllene oxide Limonene Various adjunctive role? Pinene</p>
 <p>tetrahydrocannabivarin</p>	<p>AI/anti-hyperalgesic (Bolognini <i>et al.</i>, 2010) Treatment of metabolic syndrome (Cawthorne <i>et al.</i>, 2007) Anticonvulsant (Hill <i>et al.</i>, 2010)</p>	<p>Caryophyllene <i>et al.</i> . . . – Linalool</p>
 <p>cannabidivarin</p>	<p>Inhibits diacylglycerol lipase (De Petrocellis <i>et al.</i>, 2011) Anticonvulsant in hippocampus (Hill <i>et al.</i>, 2010)</p>	<p>– Linalool</p>
 <p>cannabinal (CBN)</p>	<p>Sedative (Musty <i>et al.</i>, 1976) Effective versus MRSA (Appendino <i>et al.</i>, 2008) TRPV2 agonist for burns (Qin <i>et al.</i>, 2008) ↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007) ↓ breast cancer resistance protein (Holland <i>et al.</i>, 2008)</p>	<p>Nerolidol, myrcene Pinene Linalool adjunctive role? Limonene</p>

5-HT, 5-hydroxytryptamine (serotonin); AEA, arachidonylethanolamide (anandamide); AI, anti-inflammatory; CB₁/CB₂, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; TRPV, transient receptor potential vanilloid receptor; MRSA, methicillin-resistant *Staphylococcus aureus*; Sx, symptoms.

THC (Table 1) is the most common phytocannabinoid in cannabis drug chemotypes, and is produced in the plant via an allele co-dominant with CBD (de Meijer *et al.*, 2003). THC is a partial agonist at CB₁ and cannabinoid receptor 2 (CB₂) analogous to AEA, and underlying many of its activities as a psychoactive agent, analgesic, muscle relaxant and antispasmodic (Pacher *et al.*, 2006). Additionally, it is a bronchodilator (Williams *et al.*, 1976), neuroprotective antioxidant (Hampson *et al.*, 1998), antipruritic agent in cholestatic jaundice (Neff *et al.*, 2002) and has 20 times the anti-inflammatory power of aspirin and twice that of hydrocortisone (Evans, 1991). THC is likely to avoid potential pitfalls of either COX-1 or COX-2 inhibition, as such activity is only noted at concentrations far above those attained therapeutically (Stott *et al.*, 2005).

CBD is the most common phytocannabinoid in fibre (hemp) plants, and second most prevalent in some drug chemotypes. It has proven extremely versatile pharmacologically (Table 1) (Pertwee, 2004; Mechoulam *et al.*, 2007), displaying the unusual ability to antagonize CB₁ at a low nM level in the presence of THC, despite having little binding affinity (Thomas *et al.*, 2007), and supporting its modulatory effect on THC-associated adverse events such as anxiety, tachycardia, hunger and sedation in rats and humans (Nicholson *et al.*, 2004; Murillo-Rodriguez *et al.*, 2006; Russo and Guy, 2006). CBD is an analgesic (Costa *et al.*, 2007), is a neuroprotective antioxidant more potent than ascorbate or tocopherol (Hampson *et al.*, 1998), without COX inhibition (Stott *et al.*, 2005), acts as a TRPV1 agonist analogous to capsaicin but without noxious effect (Bisogno *et al.*, 2001), while also inhibiting uptake of AEA and weakly inhibiting its hydrolysis. CBD is an antagonist on GPR55, and also on GPR18, possibly supporting a therapeutic role in disorders of cell migration, notably endometriosis (McHugh *et al.*, 2010). CBD is anticonvulsant (Carlini and Cunha, 1981; Jones *et al.*, 2010), anti-nausea (Parker *et al.*, 2002), cytotoxic in breast cancer (Ligresti *et al.*, 2006) and many other cell lines while being cyto-preservative for normal cells (Parolaro and Massi, 2008), antagonizes tumour necrosis factor- α (TNF- α) in a rodent model of rheumatoid arthritis (Malfait *et al.*, 2000), enhances adenosine receptor A_{2A} signalling via inhibition of an adenosine transporter (Carrier *et al.*, 2006), and prevents prion accumulation and neuronal toxicity (Dirikoc *et al.*, 2007). A CBD extract showed greater anti-hyperalgesia over pure compound in a rat model with decreased allodynia, improved thermal perception and nerve growth factor levels and decreased oxidative damage (Comelli *et al.*, 2009). CBD also displayed powerful activity against methicillin-resistant *Staphylococcus aureus* (MRSA), with a minimum inhibitory concentration (MIC) of 0.5–2 $\mu\text{g}\cdot\text{mL}^{-1}$ (Appendino *et al.*, 2008). In 2005, it was demonstrated that CBD has agonistic activity at 5-hydroxytryptamine (5-HT)_{1A} at 16 μM (Russo *et al.*, 2005), and that despite the high concentration, may underlie its anti-anxiety activity (Resstel *et al.*, 2009; Soares Vde *et al.*, 2010), reduction of stroke risk (Mishima *et al.*, 2005), anti-nausea effects (Rock *et al.*, 2009) and ability to affect improvement in cognition in a mouse model of hepatic encephalopathy (Magen *et al.*, 2009). A recent study has demonstrated that CBD 30 $\text{mg}\cdot\text{kg}^{-1}$ i.p. reduced immobility time in the forced swim test compared to imipramine ($P < 0.01$), an effect blocked by pre-treatment with the 5-HT_{1A} antagonist

WAY100635 (Zanelati *et al.*, 2010), supporting a prospective role for CBD as an antidepressant. CBD also inhibits synthesis of lipids in sebocytes, and produces apoptosis at higher doses in a model of acne (*vide infra*). One example of CBD antagonism to THC would be the recent observation of lymphopenia in rats (CBD 5 $\text{mg}\cdot\text{kg}^{-1}$) mediated by possible CB₂ inverse agonism (Ignatowska-Jankowska *et al.*, 2009), an effect not reported in humans even at doses of pure CBD up to 800 mg (Crippa *et al.*, 2010), possibly due to marked interspecies differences in CB₂ sequences and signal transduction. CBD proved to be a critical factor in the ability of nabiximols oromucosal extract in successfully treating intractable cancer pain patients unresponsive to opioids (30% reduction in pain from baseline), as a high-THC extract devoid of CBD failed to distinguish from placebo (Johnson *et al.*, 2010). This may represent true synergy if the THC–CBD combination were shown to provide a larger effect than a summation of those from the compounds separately (Berenbaum, 1989).

CBC (Table 1) was inactive on adenylate cyclase inhibition (Howlett, 1987), but showed activity in the mouse cannabinoid tetrad, but only at 100 $\text{mg}\cdot\text{kg}^{-1}$, and at a fraction of THC activity, via a non-CB₁, non-CB₂ mechanism (Delong *et al.*, 2010). More pertinent are anti-inflammatory (Wirth *et al.*, 1980) and analgesic activity (Davis and Hatoum, 1983), its ability to reduce THC intoxication in mice (Hatoum *et al.*, 1981), antibiotic and antifungal effects (ElSohly *et al.*, 1982), and observed cytotoxicity in cancer cell lines (Ligresti *et al.*, 2006). A CBC-extract displayed pronounced antidepressant effect in rodent models (Deyo and Musty, 2003). Additionally, CBC was comparable to mustard oil in stimulating TRPA1-mediated Ca²⁺ in human embryonic kidney 293 cells (50–60 nM) (De Petrocellis *et al.*, 2008). CBC recently proved to be a strong AEA uptake inhibitor (De Petrocellis *et al.*, 2011). CBC production is normally maximal, earlier in the plant's life cycle (de Meijer *et al.*, 2009a). An innovative technique employing cold water extraction of immature leaf matter from selectively bred cannabis chemotypes yields a high-CBC 'enriched trichome preparation' (Potter, 2009).

CBG (Table 1), the parent phytocannabinoid compound, has a relatively weak partial agonistic effect at CB₁ (K_i 440 nM) and CB₂ (K_i 337 nM) (Gauson *et al.*, 2007). Older work supports gamma aminobutyric acid (GABA) uptake inhibition greater than THC or CBD (Banerjee *et al.*, 1975) that could suggest muscle relaxant properties. Analgesic and anti-erythemic effects and the ability to block lipooxygenase were said to surpass those of THC (Evans, 1991). CBG demonstrated modest antifungal effects (ElSohly *et al.*, 1982). More recently, it proved to be an effective cytotoxic in high dosage on human epithelioid carcinoma (Baek *et al.*, 1998), is the next most effective phytocannabinoid against breast cancer after CBD (Ligresti *et al.*, 2006), is an antidepressant in the rodent tail suspension model (Musty and Deyo, 2006) and is a mildly anti-hypertensive agent (Maor *et al.*, 2006). Additionally, CBG inhibits keratinocyte proliferation suggesting utility in psoriasis (Wilkinson and Williamson, 2007), it is a relatively potent TRPM8 antagonist for possible application in prostate cancer (De Petrocellis and Di Marzo, 2010) and detrusor over-activity and bladder pain (Mukerji *et al.*, 2006). It is a strong AEA uptake inhibitor (De Petrocellis *et al.*, 2011) and a powerful agent against MRSA (Appendino *et al.*, 2008; *vide infra*). Finally, CBG behaves as a potent α -2 adrenorecep-

tor agonist, supporting analgesic effects previously noted (Formukong *et al.*, 1988), and moderate 5-HT_{1A} antagonist suggesting antidepressant properties (Cascio *et al.*, 2010). Normally, CBG appears as a relatively low concentration intermediate in the plant, but recent breeding work has yielded cannabis chemotypes lacking in downstream enzymes that express 100% of their phytocannabinoid content as CBG (de Meijer and Hammond, 2005; de Meijer *et al.*, 2009a).

THCV (Table 1) is a propyl analogue of THC, and can modulate intoxication of the latter, displaying 25% of its potency in early testing (Gill *et al.*, 1970; Hollister, 1974). A recrudescence of interest accrues to this compound, which is a CB₁ antagonist at lower doses (Thomas *et al.*, 2005), but is a CB₁ agonist at higher doses (Pertwee, 2008). THCV produces weight loss, decreased body fat and serum leptin concentrations with increased energy expenditure in obese mice (Cawthorne *et al.*, 2007; Riedel *et al.*, 2009). THCV also demonstrates prominent anticonvulsant properties in rodent cerebellum and pyriform cortex (Hill *et al.*, 2010). THCV appears as a fractional component of many southern African cannabis chemotypes, although plants highly predominant in this agent have been produced (de Meijer, 2004). THCV recently demonstrated a CB₂-based ability to suppress carageenan-induced hyperalgesia and inflammation, and both phases of formalin-induced pain behaviour via CB₁ and CB₂ in mice (Bolognini *et al.*, 2010).

CBDV (Table 1), the propyl analogue of CBD, was first isolated in 1969 (Vollner *et al.*, 1969), but formerly received little investigation. Pure CBDV inhibits diacylglycerol lipase [50% inhibitory concentration (IC₅₀) 16.6 µM] and might decrease activity of its product, the endocannabinoid, 2-AG (De Petrocellis *et al.*, 2011). It is also anticonvulsant in rodent hippocampal brain slices, comparable to phenobarbitone and felbamate (Jones *et al.*, 2010).

Finally, CBN is a non-enzymatic oxidative by-product of THC, more prominent in aged cannabis samples (Merzouki and Mesa, 2002). It has a lower affinity for CB₁ (K_i 211.2 nM) and CB₂ (K_i 126.4 nM) (Rhee *et al.*, 1997); and was judged inactive when tested alone in human volunteers, but produced greater sedation combined with THC (Musty *et al.*, 1976). CBN demonstrated anticonvulsant (Turner *et al.*, 1980), anti-inflammatory (Evans, 1991) and potent effects against MRSA (MIC 1 µg·mL⁻¹). CBN is a TRPV2 (high-threshold thermosensor) agonist (EC 77.7 µM) of possible interest in treatment of burns (Qin *et al.*, 2008). Like CBG, it inhibits keratinocyte proliferation (Wilkinson and Williamson, 2007), independently of cannabinoid receptor effects. CBN stimulates the recruitment of quiescent mesenchymal stem cells in marrow (10 µM), suggesting promotion of bone formation (Scutt and Williamson, 2007) and inhibits breast cancer resistance protein, albeit at a very high concentration (IC₅₀ 145 µM) (Holland *et al.*, 2008).

Cannabis terpenoids: neglected entourage compounds?

Terpenoids are EO components, previously conceived as the quintessential fifth element, 'life force' or spirit (Schmidt,

2010), and form the largest group of plant chemicals, with 15–20 000 fully characterized (Langenheim, 1994). Terpenoids, not cannabinoids, are responsible for the aroma of cannabis. Over 200 have been reported in the plant (Hendriks *et al.*, 1975; 1977; Malingre *et al.*, 1975; Davalos *et al.*, 1977; Ross and ElSohly, 1996; Mediavilla and Steinemann, 1997; Rothschild *et al.*, 2005; Brenneisen, 2007), but only a few studies have concentrated on their pharmacology (McPartland and Pruitt, 1999; McPartland and Mediavilla, 2001a; McPartland and Russo, 2001b). Their yield is less than 1% in most cannabis assays, but they may represent 10% of trichome content (Potter, 2009). Monoterpenes usually predominate (limonene, myrcene, pinene), but these headspace volatiles (Hood *et al.*, 1973), while only lost at a rate of about 5% before processing (Gershenson, 1994), do suffer diminished yields with drying and storage (Turner *et al.*, 1980; Ross and ElSohly, 1996), resulting in a higher relative proportion of sesquiterpenoids (especially caryophyllene), as also often occurs in extracts. A 'phytochemical polymorphism' seems operative in the plant (Franz and Novak, 2010), as production favours agents such as limonene and pinene in flowers that are repellent to insects (Nerio *et al.*, 2010), while lower fan leaves express higher concentrations of bitter sesquiterpenoids that act as anti-feedants for grazing animals (Potter, 2009). Evolutionarily, terpenoids seem to occur in complex and variable mixtures with marked structural diversity to serve various ecological roles. Terpenoid composition is under genetic control (Langenheim, 1994), and some enzymes produce multiple products, again supporting Mechoulam's 'Law of Stinginess'. The particular mixture of mono- and sesquiterpenoids will determine viscosity, and in cannabis, this certainly is leveraged to practical advantage as the notable stickiness of cannabis exudations traps insects (McPartland *et al.*, 2000), and thus, combined with the insecticidal phytocannabinoid acids (Sirikantaramas *et al.*, 2005), provides a synergistic mechano-chemical defensive strategy versus predators.

As observed for cannabinoids, terpenoid production increases with light exposure, but decreases with soil fertility (Langenheim, 1994), and this is supported by the glasshouse experience that demonstrates higher yields if plants experience relative nitrogen lack just prior to harvest (Potter, 2004), favouring floral over foliar growth. EO composition is much more genetically than environmentally determined, however (Franz and Novak, 2010), and while cannabis is allogamous and normally requires repeat selective breeding for maintenance of quality, this problem may be practically circumvented by vegetative propagation of high-performance plants under controlled environmental conditions (light, heat and humidity) (Potter, 2009), and such techniques have proven to provide notable consistency to tight tolerances as Good Manufacturing Practice for any pharmaceutical would require (Fischedick *et al.*, 2010).

The *European Pharmacopoeia*, Sixth Edition (2007), lists 28 EOs (Pauli and Schilcher, 2010). Terpenoids are pharmacologically versatile: they are lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled (odorant) receptors, second messenger systems and enzymes (Bowles, 2003; Buchbauer, 2010). All the terpenoids discussed herein are Generally Recognized as Safe, as attested by the US Food and Drug Admin-

istration as food additives, or by the Food and Extract Manufacturers Association and other world regulatory bodies. Germane is the observation (Adams and Taylor, 2010) (p. 193), 'With a high degree of confidence one may presume that EOs derived from food are likely to be safe'. Additionally, all the current entries are non-sensitizing to skin when fresh (Tisserand and Balacs, 1995; Adams and Taylor, 2010), but may cause allergic reactions at very low rates when oxidized (Matura *et al.*, 2005). For additional pharmacological data on other common cannabis terpenoids not discussed herein (1,8-cineole, also known as eucalyptol, pulegone, α -terpineol, terpineol-4-ol, p -cymene, borneol and Δ -3-carene), please see McPartland and Russo (2001b).

Are cannabis terpenoids actually relevant to the effects of cannabis? Terpenoid components in concentrations above 0.05% are considered of pharmacological interest (Adams and Taylor, 2010). Animal studies are certainly supportive (Buchbauer *et al.*, 1993). Mice exposed to terpenoid odours inhaled from ambient air for 1 h demonstrated profound effects on activity levels, suggesting a direct pharmacological effect on the brain, even at extremely low serum concentrations (examples: linalool with 73% reduction in motility at 4.22 ng·mL⁻¹, pinene 13.77% increase at trace concentration, terpineol 45% reduction at 4.7 ng·mL⁻¹). These levels are comparable to those of THC measured in humans receiving cannabis extracts yielding therapeutic effects in pain, or symptoms of multiple sclerosis in various randomized controlled trials (RCTs) (Russo, 2006; Huestis, 2007). Positive effects at undetectable serum concentrations with orange terpenes (primarily limonene, 35.25% increase in mouse activity), could be explainable on the basis of rapid redistribution and concentration in lipophilic cerebral structures. A similar rationale pertains to human studies (Komori *et al.*, 1995), subsequently discussed. Limonene is highly bioavailable with 70% human pulmonary uptake (Falk-Filipsson *et al.*, 1993), and a figure of 60% for pinene with rapid metabolism or redistribution (Falk *et al.*, 1990). Ingestion and percutaneous absorption is also well documented in humans (Jäger *et al.*, 1992): 1500 mg of lavender EO with 24.7% linalool (total 372 mg) was massaged into the skin of a 60 kg man for 10 min, resulting in a peak plasma concentration of 100 ng·mL⁻¹ at 19 min, and a half-life of 13.76 min in serum (Jäger *et al.*, 1992). EO mixtures (including limonene and pinene) also increase permeation of estradiol through mouse skin (Monti *et al.*, 2002).

Government-approved cannabis supplied to patients in national programmes in the Netherlands and Canada is gamma-irradiated to sterilize coliform bacteria, but the safety of this technique for a smoked and inhaled product has never been specifically tested. Gamma-radiation significantly reduced linalool titres in fresh cilantro (Fan and Sokorai, 2002), and myrcene and linalool in orange juice (Fan and Gates, 2001).

D-limonene, common to the lemon and other citrus EOs (Table 2), is the second most widely distributed terpenoid in nature (Noma and Asakawa, 2010), and is the precursor to other monoterpenoids (Figure 2) through species-specific synthetic schemes. Unfortunately, these pathways have not yet been investigated in cannabis. The ubiquity of limonene serves, perhaps, as a demonstration of convergent evolution that supports an important ecological role for this monoter-

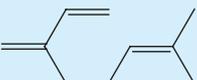
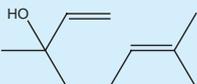
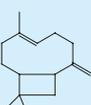
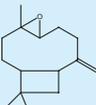
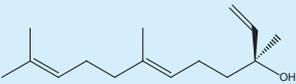
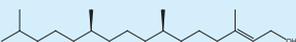
pene. Studies with varying methodology and dosing in citrus oils in mice suggest it to be a powerful anxiolytic agent (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006), with one EO increasing serotonin in the prefrontal cortex, and dopamine (DA) in hippocampus mediated via 5-HT_{1A} (Komiya *et al.*, 2006). Compelling confirmatory evidence in humans was provided in a clinical study (Komori *et al.*, 1995), in which hospitalized depressed patients were exposed to citrus fragrance in ambient air, with subsequent normalization of Hamilton Depression Scores, successful discontinuation of antidepressant medication in 9/12 patients and serum evidence of immune stimulation (CD4/8 ratio normalization). Limonene also produces apoptosis of breast cancer cells, and was employed at high doses in Phase II RCTs (Vigushin *et al.*, 1998). Subsequent investigation in cancer treatment has centred on its immediate hepatic metabolite, perillic acid, which demonstrates anti-stress effects in rat brain (Fukumoto *et al.*, 2008). A patent has been submitted, claiming that limonene effectively treats gastro-oesophageal reflux (Harris, 2010). Citrus EOs containing limonene proved effective against dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010), and citrus EOs with terpenoid profiles resembling those in cannabis demonstrated strong radical scavenging properties (Choi *et al.*, 2000). As noted above, limonene is highly bioavailable (Falk-Filipsson *et al.*, 1993), and rapidly metabolized, but with indications of accumulation and retention in adipose tissues (e.g. brain). It is highly non-toxic (estimated human lethal dose 0.5–5 g·kg⁻¹) and non-sensitizing (Von Burg, 1995).

β -Myrcene is another common monoterpene in cannabis (Table 2) with myriad activities: diminishing inflammation via prostaglandin E-2 (PGE-2) (Lorenzetti *et al.*, 1991), and blocking hepatic carcinogenesis by aflatoxin (De-Oliveira *et al.*, 1997). Interestingly, myrcene is analgesic in mice, but this action can be blocked by naloxone, perhaps via the α -2 adrenoreceptor (Rao *et al.*, 1990). It is non-mutagenic in the Ames test (Gomes-Carneiro *et al.*, 2005). Myrcene is a recognized sedative as part of hops preparations (*Humulus lupulus*), employed to aid sleep in Germany (Bisset and Wichtl, 2004). Furthermore, myrcene acted as a muscle relaxant in mice, and potentiated barbiturate sleep time at high doses (do Vale *et al.*, 2002). Together, these data would support the hypothesis that myrcene is a prominent sedative terpenoid in cannabis, and combined with THC, may produce the 'couch-lock' phenomenon of certain chemotypes that is alternatively decried or appreciated by recreational cannabis consumers.

α -Pinene is a bicyclic monoterpene (Table 2), and the most widely encountered terpenoid in nature (Noma and Asakawa, 2010). It appears in conifers and innumerable plant EOs, with an insect-repellent role. It is anti-inflammatory via PGE-1 (Gil *et al.*, 1989), and is a bronchodilator in humans at low exposure levels (Falk *et al.*, 1990). Pinene is a major component of *Sideritis* spp. (Kose *et al.*, 2010) and *Salvia* spp. EOs (Ozek *et al.*, 2010), both with prominent activity against MRSA (*vide infra*). Beyond this, it seems to be a broad-spectrum antibiotic (Nissen *et al.*, 2010). α -Pinene forms the biosynthetic base for CB₂ ligands, such as HU-308 (Hanus *et al.*, 1999). Perhaps most compelling, however, is its activity as an acetylcholinesterase inhibitor aiding memory (Perry *et al.*, 2000), with an observed IC₅₀ of 0.44 mM (Miyazawa

Table 2

Cannabis Terpenoid Activity Table

Terpenoid	Structure	Commonly encountered in	Pharmacological activity (Reference)	Synergistic cannabinoid
Limonene		 Lemon	Potent AD/immunostimulant via inhalation (Komori <i>et al.</i> , 1995) Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultrini Ade <i>et al.</i> , 2006) via 5-HT _{1A} (Komiya <i>et al.</i> , 2006) Apoptosis of breast cancer cells (Vigushin <i>et al.</i> , 1998) Active against acne bacteria (Kim <i>et al.</i> , 2008) Dermatophytes (Sanguinetti <i>et al.</i> , 2007; Singh <i>et al.</i> , 2010) Gastro-oesophageal reflux (Harris, 2010)	CBD CBD CBD, CBG CBD CBG THC
α -Pinene		 Pine	Anti-inflammatory via PGE-1 (Gil <i>et al.</i> , 1989) Bronchodilatory in humans (Falk <i>et al.</i> , 1990) Acetylcholinesterase inhibitor, aiding memory (Perry <i>et al.</i> , 2000)	CBD THC THC?, CBD
β -Myrcene		 Hops	Blocks inflammation via PGE-2 (Lorenzetti <i>et al.</i> , 1991) Analgesic, antagonized by naloxone (Rao <i>et al.</i> , 1990) Sedating, muscle relaxant, hypnotic (do Vale <i>et al.</i> , 2002) Blocks hepatic carcinogenesis by aflatoxin (de Oliveira <i>et al.</i> , 1997)	CBD CBD, THC THC CBD, CBG
Linalool		 Lavender	Anti-anxiety (Russo, 2001) Sedative on inhalation in mice (Buchbauer <i>et al.</i> , 1993) Local anesthetic (Re <i>et al.</i> , 2000) Analgesic via adenosine A _{2A} (Peana <i>et al.</i> , 2006) Anticonvulsant/anti-glutamate (Elisabetsky <i>et al.</i> , 1995) Potent anti-leishmanial (do Socorro <i>et al.</i> , 2003)	CBD, CBG? THC THC CBD CBD, THCV, CBDV ?
β -Caryophyllene		 Pepper	AI via PGE-1 comparable phenylbutazone (Basile <i>et al.</i> , 1988) Gastric cytoprotective (Tambe <i>et al.</i> , 1996) Anti-malarial (Campbell <i>et al.</i> , 1997) Selective CB ₂ agonist (100 nM) (Gertsch <i>et al.</i> , 2008) Treatment of pruritus? (Karsak <i>et al.</i> , 2007) Treatment of addiction? (Xi <i>et al.</i> , 2010)	CBD THC ? THC THC CBD
Caryophyllene Oxide		 Lemon balm	Decreases platelet aggregation (Lin <i>et al.</i> , 2003) Antifungal in onychomycosis comparable to ciclopiroxolamine and sulconazole (Yang <i>et al.</i> , 1999) Insecticidal/anti-feedant (Bettarini <i>et al.</i> , 1993)	THC CBC, CBG THCA, CBGA
Nerolidol		 Orange	Sedative (Binet <i>et al.</i> , 1972) Skin penetrant (Cornwell and Barry, 1994) Potent antimalarial (Lopes <i>et al.</i> , 1999, Rodrigues Goulart <i>et al.</i> , 2004) Anti-leishmanial activity (Arruda <i>et al.</i> , 2005)	THC, CBN – ? ?
Phytol		 Green tea	Breakdown product of chlorophyll Prevents Vitamin A teratogenesis (Arnhold <i>et al.</i> , 2002) \uparrow GABA via SSADH inhibition (Bang <i>et al.</i> , 2002)	– – CBG

Representative plants containing each terpenoid are displayed as examples to promote recognition, but many species contain them in varying concentrations. 5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; AI, anti-inflammatory; CB₁/CB₂, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; PGE-1/PGE-2, prostaglandin E-1/prostaglandin E-2; SSADH, succinic semialdehyde dehydrogenase.

and Yamafuji, 2005). This feature could counteract short-term memory deficits induced by THC intoxication (*vide infra*).

D-Linalool is a monoterpenoid alcohol (Table 2), common to lavender (*Lavandula angustifolia*), whose psychotropic anxiolytic activity has been reviewed in detail (Russo, 2001). Interestingly, linalyl acetate, the other primary terpenoid in lavender, hydrolyses to linalool in gastric secretions (Bickers *et al.*, 2003). Linalool proved sedating to mouse activity on inhalation (Buchbauer *et al.*, 1991; Jirovetz *et al.*, 1992). In traditional aromatherapy, linalool is the likely suspect in the remarkable therapeutic capabilities of lavender EO to alleviate skin burns without scarring (Gattefosse, 1993). Pertinent to this, the local anaesthetic effects of linalool (Re *et al.*, 2000) are equal to those of procaine and menthol (Ghelardini *et al.*, 1999). Another explanation would be its ability to produce hot-plate analgesia in mice ($P < 0.001$) that was reduced by administration of an adenosine A_{2A} antagonist (Peana *et al.*, 2006). It is also anti-nociceptive at high doses in mice via ionotropic glutamate receptors (Batista *et al.*, 2008). Linalool demonstrated anticonvulsant and anti-glutamatergic activity (Elisabetsky *et al.*, 1995), and reduced seizures as part of *Ocimum basilicum* EO after exposure to pentylenetetrazole, picrotoxin and strychnine (Ismail, 2006). Furthermore, linalool decreased K^+ -stimulated glutamate release and uptake in mouse synaptosomes (Silva Brum *et al.*, 2001). These effects were summarized (Nunes *et al.*, 2010, p. 303): 'Overall, it seems reasonable to argue that the modulation of glutamate and GABA neurotransmitter systems are likely to be the critical mechanism responsible for the sedative, anxiolytic and anticonvulsant properties of linalool and EOs containing linalool in significant proportions'. Linalool also proved to be a powerful anti-leishmanial agent (do Socorro *et al.*, 2003), and as a presumed lavender EO component, decreased morphine opioid usage after inhalation versus placebo ($P = 0.04$) in gastric banding in morbidly obese surgical patients (Kim *et al.*, 2007).

β -Caryophyllene (Table 2) is generally the most common sesquiterpenoid encountered in cannabis (Mediavilla and Steinemann, 1997), wherein its evolutionary function may be due to its ability to attract insect predatory green lacewings, while simultaneously inhibiting insect herbivory (Langenheim, 1994). It is frequently the predominant terpenoid overall in cannabis extracts, particularly if they have been processed under heat for decarboxylation (Guy and Stott, 2005). Caryophyllene is common to black pepper (*Piper nigrum*) and Copaiba balsam (*Copaifera officinalis*) (Lawless, 1995). It is anti-inflammatory via PGE-1, comparable in potency to the toxic phenylbutazone (Basile *et al.*, 1988), and an EO containing it was on par with etodolac and indomethacin (Ozturk and Ozbek, 2005). In contrast to the latter agents, however, caryophyllene was a gastric cytoprotective (Tambe *et al.*, 1996), much as had been claimed in the past in treating duodenal ulcers in the UK with cannabis extract (Douthwaite, 1947). Caryophyllene may have contributed to anti-malarial effects as an EO component (Campbell *et al.*, 1997). Perhaps the greatest revelation regarding caryophyllene has been its demonstration as a selective full agonist at CB_2 (100 nM), the first proven phytocannabinoid beyond the cannabis genus (Gertsch *et al.*, 2008). Subsequent work has demonstrated that this dietary component produced anti-inflammatory analgesic activity at the lowest dose of

5 mg·kg⁻¹ in wild-type, but not CB_2 knockout mice (Gertsch, 2008). Given the lack of attributed psychoactivity of CB_2 agonists, caryophyllene offers great promise as a therapeutic compound, whether systemically, or in dermatological applications such as contact dermatitis (Karsak *et al.*, 2007). Sensitization reactions are quite rare, and probably due to oxidized product (Skold *et al.*, 2006).

Nerolidol is a sesquiterpene alcohol with sedative properties (Binet *et al.*, 1972), present as a low-level component in orange and other citrus peels (Table 2). It diminished experimentally induced formation of colon adenomas in rats (Wattenberg, 1991). It was an effective agent for enhancing skin penetration of 5-fluorouracil (Cornwell and Barry, 1994). This could be a helpful property in treating fungal growth, where it is also an inhibitor (Langenheim, 1994). It seems to have anti-protozoal parasite control benefits, as a potent antimalarial (Lopes *et al.*, 1999; Rodrigues Goulart *et al.*, 2004) and anti-leishmanial agent (Arruda *et al.*, 2005). Nerolidol is non-toxic and non-sensitizing (Lapczynski *et al.*, 2008).

Caryophyllene oxide (Table 2) is a sesquiterpenoid oxide common to lemon balm (*Melissa officinalis*), and to the eucalyptus, *Melaleuca stypheloides*, whose EO contains 43.8% (Farag *et al.*, 2004). In the plant, it serves as an insecticidal/anti-feedant (Bettarini *et al.*, 1993) and as broad-spectrum antifungal in plant defence (Langenheim, 1994). Analogously, the latter properties may prove therapeutic, as caryophyllene oxide demonstrated antifungal efficacy in a model of clinical onychomycosis comparable to ciclopiroxamine and sulconazole, with an 8% concentration affecting eradication in 15 days (Yang *et al.*, 1999). Caryophyllene oxide is non-toxic and non-sensitizing (Opdyke, 1983). This agent also demonstrates anti-platelet aggregation properties *in vitro* (Lin *et al.*, 2003). Caryophyllene oxide has the distinction of being the component responsible for cannabis identification by drug-sniffing dogs (Stahl and Kunde, 1973).

Phytol (Table 2) is a diterpene (McGinty *et al.*, 2010), present in cannabis extracts, as a breakdown product of chlorophyll and tocopherol. Phytol prevented vitamin A-induced teratogenesis by inhibiting conversion of retinol to a harmful metabolite, all-*trans*-retinoic acid (Arnhold *et al.*, 2002). Phytol increased GABA expression via inhibition of succinic semialdehyde dehydrogenase, one of its degradative enzymes (Bang *et al.*, 2002). Thus, the presence of phytol could account for the alleged relaxing effect of wild lettuce (*Lactuca sativa*), or green tea (*Camellia sinensis*), despite the latter's caffeine content.

Selected possibilities for phytocannabinoid-terpenoid synergy

Cannabis and acne

AEA simulates lipid production in human sebocytes of sebaceous glands at low concentrations, but induces apoptosis at higher levels, suggesting that this system is under ECS control (Dobrosi *et al.*, 2008). CBD 10–20 μ M did not affect basal lipid synthesis in SZ95 sebocytes, but did block such stimulation by AEA and arachidonate (Biro *et al.*, 2009). Higher doses of CBD (30–50 μ M) induced sebocyte apoptosis, which was augmented in the presence of AEA. The effect of CBD to increase

Ca⁺⁺ was blocked by ruthenium red, a TRP-inhibitor. RNA-mediated silencing of TRPV1 and TRPV3 failed to attenuate CBD effects, but experiments did support the aetiological role of TRPV4, a putative regulator of systemic osmotic pressure (T. Bíró, 2010, pers. comm.). Given the observed ability of CBD to be absorbed transcutaneously, it offers great promise to attenuate the increased sebum production at the pathological root of acne.

Cannabis terpenoids could offer complementary activity. Two citrus EOs primarily composed of limonene inhibited *Propionibacterium acnes*, the key pathogen in acne (MIC 0.31 $\mu\text{L}\cdot\text{mL}^{-1}$), more potently than triclosan (Kim *et al.*, 2008). Linalool alone demonstrated an MIC of 0.625 $\mu\text{L}\cdot\text{mL}^{-1}$. Both EOs inhibited *P. acnes*-induced TNF- α production, suggesting an adjunctive anti-inflammatory effect. In a similar manner, pinene was the most potent component of a tea-tree eucalyptus EO in suppression of *P. acnes* and *Staph* spp. in another report (Raman *et al.*, 1995).

Considering the known minimal toxicities of CBD and these terpenoids and the above findings, new acne therapies utilizing whole CBD-predominant extracts, via multi-targeting (Wagner and Ulrich-Merzenich, 2009), may present a novel and promising therapeutic approach that poses minimal risks in comparison to isotretinoin.

MRSA

MRSA accounted for 10% of cases of septicaemia and 18 650 deaths in the USA in 2005, a number greater than that attributable to human immunodeficiency virus/acquired immunodeficiency syndrome (Bancroft, 2007). Pure CBD and CBG powerfully inhibit MRSA (MIC 0.5–2 $\mu\text{g}\cdot\text{mL}^{-1}$) (Appendino *et al.*, 2008).

Amongst terpenoids, pinene was a major component of *Sideritis erythrantha* EO that was as effective against MRSA and other antibiotic-resistant bacterial strains as vancomycin and other agents (Kose *et al.*, 2010). A *Salvia rosifolia* EO with 34.8% pinene was also effective against MRSA (MIC 125 $\mu\text{g}\cdot\text{mL}^{-1}$). The ability of monoterpenoids to enhance skin permeability and entry of other drugs may further enhance antibiotic benefits (Wagner and Ulrich-Merzenich, 2009).

Given that CBG can be produced in selected cannabis chemotypes (de Meijer and Hammond, 2005; de Meijer *et al.*, 2009a), with no residual THC as a possible drug abuse liability risk, a whole plant extract of a CBG-chemotype also expressing pinene would seem to offer an excellent, safe new anti-septic agent.

Psychopharmacological applications: depression, anxiety, insomnia, dementia and addiction

Scientific investigation of the therapeutic application of terpenoids in psychiatry has been hampered by methodological concerns, subjective variability of results and a genuine dearth of appropriate randomized controlled studies of high quality (Russo, 2001; Bowles, 2003; Lis-Balchin, 2010). The

same is true of phytocannabinoids (Fride and Russo, 2006). Abundant evidence supports the key role of the ECS in mediating depression (Hill and Gorzalka, 2005a,b), as well as anxiety, whether induced by aversive stimuli, such as post-traumatic stress disorder (Marsicano *et al.*, 2002) or pain (Hohmann *et al.*, 2005), and psychosis (Giuffrida *et al.*, 2004). With respect to the latter risk, the presence of CBD in smoked cannabis based on hair analysis seems to be a mitigating factor reducing its observed incidence (Morgan and Curran, 2008). A thorough review of cannabis and psychiatry is beyond the scope of this article, but several suggestions are offered with respect to possible therapeutic synergies operative with phytocannabinoids-terpenoid combinations. While the possible benefits of THC on depression remain controversial (Denson and Earleywine, 2006), much less worrisome would be CBD- or CBG-predominant preparations. Certainly the results obtained in human depression solely with a citrus scent (Komori *et al.*, 1995), strongly suggest the possibility of synergistic benefit of a phytocannabinoid-terpenoid preparation. Enriched odour exposure in adult mice induced olfactory system neurogenesis (Rocheffort *et al.*, 2002), an intriguing result that could hypothetically support plasticity mechanisms in depression (Delgado and Moreno, 1999), and similar hypotheses with respect to the ECS in addiction treatment (Gerdeeman and Lovinger, 2003). Phytocannabinoid-terpenoid synergy might theoretically apply.

The myriad effects of CBD on 5-HT_{1A} activity provide a strong rationale for this and other phytocannabinoids as base compounds for treatment of anxiety. Newer findings, particularly imaging studies of CBD in normal individuals in anxiety models (Fusar-Poli *et al.*, 2009; 2010; Crippa *et al.*, 2010) support this hypothesis. Even more compelling is a recent randomized control trial of pure CBD in patients with social anxiety disorder with highly statistical improvements over placebo in anxiety and cognitive impairment (Crippa *et al.*, 2011). Addition of anxiolytic limonene and linalool could contribute to the clinical efficacy of a CBD extract.

THC was demonstrated effective in a small crossover clinical trial versus placebo in 11 agitated dementia patients with Alzheimer's disease (Volicer *et al.*, 1997). THC was also observed to be an acetylcholinesterase inhibitor in its own right, as well as preventing amyloid β -peptide aggregation in that disorder (Eubanks *et al.*, 2006). Certainly, the anti-anxiety and anti-psychotic effects of CBD may be of additional benefit (Zuardi *et al.*, 1991; 2006; Zuardi and Guimaraes, 1997). A recent study supports the concept that CBD, when present in significant proportion to THC, is capable of eliminating induced cognitive and memory deficits in normal subjects smoking cannabis (Morgan *et al.*, 2010b). Furthermore, CBD may also have primary benefits on reduction of β -amyloid in Alzheimer's disease (Iuvone *et al.*, 2004; Esposito *et al.*, 2006a,b). Psychopharmacological effects of limonene, pinene and linalool could putatively extend benefits in mood in such patients.

The effects of cannabis on sleep have been reviewed (Russo *et al.*, 2007), and highlight the benefits that can accrue in this regard, particularly with respect to symptom reduction permitting better sleep, as opposed to a mere hypnotic effect. Certainly, terpenoids with pain-relieving, anti-anxiety or sedative effects may supplement such activity, notably, caryophyllene, linalool and myrcene.

The issue of cannabis addiction remains controversial. Some benefit of oral THC has been noted in cannabis withdrawal (Hart *et al.*, 2002; Haney *et al.*, 2004). More intriguing, perhaps, are claims of improvement on other substance dependencies, particularly cocaine (Labigalini *et al.*, 1999; Dreher, 2002). The situation with CBD is yet more promising. CBD and THC at doses of 4 mg·kg⁻¹ i.p. potentiated extinction of cocaine- and amphetamine-induced conditioned place preference in rats, and CBD produced no hedonic effects of its own (Parker *et al.*, 2004). CBD 5 mg·kg⁻¹·d⁻¹ in rats attenuated heroin-seeking behaviour by conditioned stimuli, even after a lapse of 2 weeks (Ren *et al.*, 2009). A suggested mechanism of CBD relates to its ability to reverse changes in α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate glutamate and CB₁ receptor expression in the nucleus accumbens induced by heroin. The authors proposed CBD as a treatment for heroin craving and addiction relapse. A recent study demonstrated the fascinating result that patients with damage to the insula due to cerebrovascular accident were able to quit tobacco smoking without relapse or urges (Naqvi *et al.*, 2007), highlighting this structure as a critical neural centre mediating addiction to nicotine. Further study has confirmed the role of the insula in cocaine, alcohol and heroin addiction (Naqvi and Bechara, 2009; Naqvi and Bechara, 2010). In a provocative parallel, CBD 600 mg p.o. was demonstrated to deactivate functional magnetic resonance imaging (fMRI) activity in human volunteers in the left insula versus placebo ($P < 0.01$) without accompanying sedation or psychoactive changes (Borgwardt *et al.*, 2008), suggesting the possibility that CBD could act as a pharmaceutical surrogate for insular damage in exerting an anti-addiction therapeutic benefit. Human studies have recently demonstrated that human volunteers smoking cannabis with higher CBD content reduced their liking for drug-related stimuli, including food (Morgan *et al.*, 2010a). The authors posited that CBD can modulate reinforcing properties of drugs of abuse, and help in training to reduce relapse to alcoholism. A single case report of a successful withdrawal from cannabis dependency utilizing pure CBD treatment was recently published (Crippa *et al.*, 2010).

Perhaps terpenoids can provide adjunctive support. In a clinical trial, 48 cigarette smokers inhaling vapour from an EO of black pepper (*Piper nigrum*), a mint-menthol mixture or placebo (Rose and Behm, 1994). Black pepper EO reduced nicotine craving significantly ($P < 0.01$), an effect attributed to irritation of the bronchial tree, simulating the act of cigarette smoking, but without nicotine or actual burning of material. Rather, might not the effect have been pharmacological? The terpenoid profile of black pepper suggests possible candidates: myrcene via sedation, pinene via increased alertness, or especially caryophyllene via CB₂ agonism and a newly discovered putative mechanism of action in addiction treatment.

CB₂ is expressed in dopaminergic neurones in the ventral tegmental area and nucleus accumbens, areas mediating addictive phenomena (Xi *et al.*, 2010). Activation of CB₂ by the synthetic agonist JWH144 administered systemically, intranasally, or by microinjection into the nucleus accumbens in rats inhibited DA release and cocaine self-administration. Caryophyllene, as a high-potency selective CB₂ agonist (Gertsch *et al.*, 2008), would likely produce

similar effects, and have the advantage of being a non-toxic dietary component. All factors considered, CBD, with caryophyllene, and possibly other adjunctive terpenoids in the extract, offers significant promise in future addiction treatment.

Taming THC: cannabis entourage compounds as antidotes to intoxication

Various sources highlight the limited therapeutic index of pure THC, when given intravenously (D'Souza *et al.*, 2004) or orally (Favrat *et al.*, 2005), especially in people previously naïve to its effects. Acute overdose incidents involving THC or THC-predominant cannabis usually consist of self-limited panic reactions or toxic psychoses, for which no pharmacological intervention is generally necessary, and supportive counselling (reassurance or 'talking down') is sufficient to allow resolution without sequelae. CBD modulates the psychoactivity of THC and reduces its adverse event profile (Russo and Guy, 2006), highlighted by recent results above described. Could it be, however, that other cannabis components offer additional attenuation of the less undesirable effects of THC? History provides some clues.

In 10th century Persia, Al-Razi offered a prescription in his *Manafi al-agdhiya wa-daf madarri-ha* (p. 248), rendered (Lozano, 1993, p. 124; translation EBR) ' – and to avoid these harms {from ingestion of cannabis seeds or hashish}, one should drink fresh water and ice or eat any acid fruits'. This concept was repeated in various forms by various authorities through the ages, including ibn Sina (ibn Sina (Avicenna), 1294), and Ibn al-Baytar (ibn al-Baytar, 1291), until O'Shaughnessy brought Indian hemp to Britain in 1843 (O'Shaughnessy, 1843). Robert Christison subsequently cited lemon (Figure 3A) as an antidote to acute intoxication in numerous cases (Christison, 1851) and this excerpt regarding morning-after residua (Christison, 1848) (p. 973):

Next morning there was an ordinary appetite, much torpidity, great defect and shortness of memory, extreme apparent protraction of time, but no peculiarity of articulation or other effect; and these symptoms lasted until 2 P.M., when they ceased entirely in a few minutes after taking lemonade.

Literary icons on both sides of the Atlantic espoused similar support for the citrus cure in the 19th century, notably Bayard Taylor after travels in Syria (Taylor, 1855), and Fitzhugh Ludlow after his voluntary experiments with ever higher cannabis extract doses in the USA (Ludlow, 1857). The sentiment was repeated by Calkins (1871), who noted the suggestion of a friend in Tunis that lemon retained the confidence of cure of overdoses by cannabis users in that region. This is supported by the observation that lemon juice, which normally contains small terpenoid titres, is traditionally enhanced in North Africa by the inclusion in drinks of the limonene-rich rind, as evidenced by the recipe for *Agua Limón* from modern Morocco (Morse and Mamane, 2001). In his comprehensive review of cannabis in the first half of the 20th century, Walton once more supported its prescription (Walton, 1938).

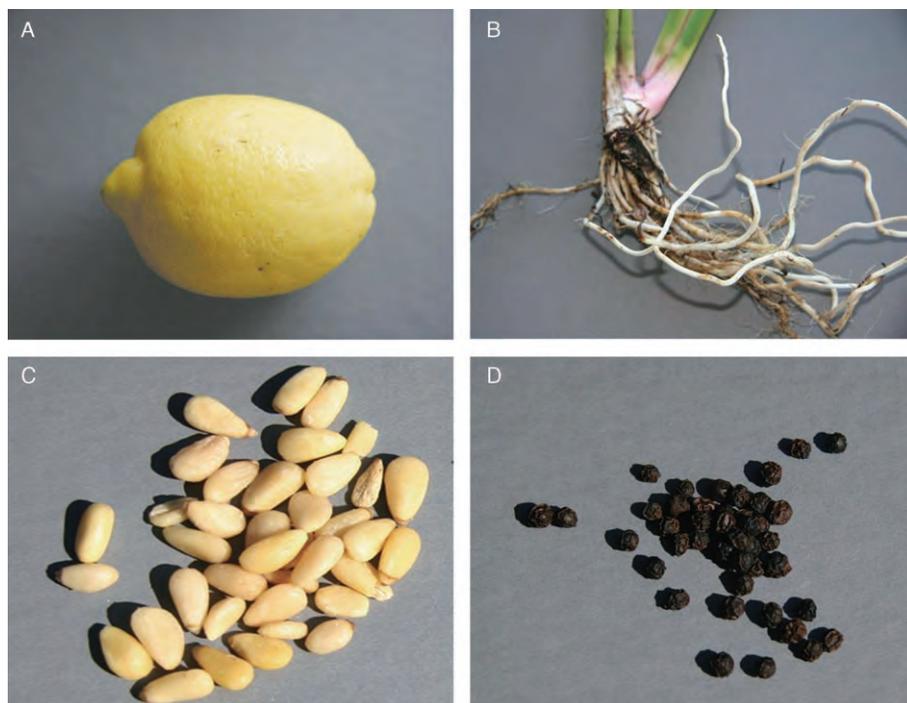


Figure 3

Ancient cannabis antidotes. (A) Lemon (*Citrus limon*). (B) Calamus plant roots (*Acorus calamus*). (C) Pine nuts (*Pinus* spp.). (D) Black pepper (*Piper nigrum*).

Another traditional antidote to cannabis employing *Acorus calamus* (Figure 3B) is evident from the Ayurvedic tradition of India (Lad, 1990, p. 131):

Calamus root is the best antidote for the ill effects of marijuana. . . . if one smokes a pinch of calamus root powder with the marijuana, this herb will completely neutralize the toxic side effects of the drug.

This claim has gained credence, not only through force of anecdotal accounts that abound on the Internet, but with formal scientific case reports and scientific analysis (McPartland *et al.*, 2008) documenting clearer thinking and improved memory with the cannabis–calamus combination, and with provision of a scientific rationale: calamus contains beta-asarone, an acetylcholinesterase inhibitor with 10% of the potency of physostigmine (Mukherjee *et al.*, 2007). Interestingly, the cannabis terpenoid, α -pinene, also has been characterized as a potent inhibitor of that enzyme (Miyazawa and Yamafuji, 2005), bolstering the hypothesis of a second antidote to THC contained in cannabis itself. Historical precedents also support pinene in this pharmacological role.

In the first century, Pliny wrote of cannabis in his *Natural History*, Book XXIV (Pliny, 1980, p. 164):

The gelotophyllis [‘leaves of laughter’ = cannabis] grows in Bactria and along the Borysthenes. If this be taken in myrrh and wine all kinds of phantoms beset the mind, causing laughter which persists until the kernels of pine-nuts are taken with pepper and honey in palm wine.

Of the components, palm wine is perhaps the most mysterious. Ethanol does not reduce cannabis intoxication (Mello

and Mendelson, 1978). However, ancient wines were stored in clay pots or goatskins, and required preservation, usually with addition of pine tar or terebinth resin (from *Pistacia* spp.; McGovern *et al.*, 2009). Pine tar is rich in pinene, as is terebinth resin (from *Pistacia terebinthus*; Tsokou *et al.*, 2007), while the latter also contains limonene (Duru *et al.*, 2003). Likewise, the pine nuts (Figure 3C) prescribed by Pliny the Elder harbour pinene, along with additional limonene (Salvadeo *et al.*, 2007). Al-Ukbari also suggested pistachio nuts as a cannabis antidote in the 13th century (Lozano, 1993), and the ripe fruits of *Pistacia terebinthus* similarly contain pinene (Couladis *et al.*, 2003). The black pepper (Figure 3D), might offer the mental clarity afforded by pinene, sedation via myrcene and helpful contributions by β -caryophyllene. The historical suggestions for cannabis antidotes are thus supported by modern scientific rationales for the claims, and if proven experimentally would provide additional evidence of synergy (Berenbaum, 1989; Wagner and Ulrich-Merzenich, 2009).

Conclusions and suggestions for future study

Considered ensemble, the preceding body of information supports the concept that selective breeding of cannabis chemotypes rich in ameliorative phytocannabinoid and terpenoid content offer complementary pharmacological activities that may strengthen and broaden clinical applications and improve the therapeutic index of cannabis extracts containing THC, or other base phytocannabinoids. Psychopharmacological and dermatological indications show the greatest promise.

One important remaining order of business is the elucidation of mono- and sesquiterpenoid biosynthetic pathways in cannabis, as has been achieved previously in other species of plants (Croteau, 1987; Gershenzon and Croteau, 1993; Bohlmann *et al.*, 1998; Turner *et al.*, 1999; Trapp and Croteau, 2001).

Various cannabis component combinations or cannabis extracts should be examined via high throughput pharmacological screening where not previously accomplished. Another goal is the investigation of the biochemical targets of the cannabis terpenoids, along with their mechanisms of action, particularly in the central nervous system. Possible techniques for such research include radio-labelling of select agents in animals with subsequent necropsy. On a molecular level, investigation of terpenoid changes to phytocannabinoid signal transduction and trafficking may prove illuminating. While it is known that terpenoids bind to odorant receptors in the nasal mucosa (Friedrich, 2004) and proximal olfactory structures (Barnea *et al.*, 2004), it would be essential to ascertain if direct effects in limbic or other cerebral structures are operative. Given that farnesyl pyrophosphate is a sesquiterpenoid precursor and the most potent endogenous agonist yet discovered for GPR92 (McHugh *et al.*, 2010), *in silico* studies attempting to match minor cannabinoids and terpenoids to orphan GPCRs may prove fruitful. Behavioural assays of agents in animal models may also provide clues. Simple combinations of phytocannabinoids and terpenoids may demonstrate synergy as antibiotics if MICs are appreciably lowered (Wagner and Ulrich-Merzenich, 2009). Ultimately, fMRI and single photon emission computed tomography studies in humans, with simultaneous drug reaction questionnaires and psychometric testing employing individual agents and phytocannabinoid-terpenoid pairings via vaporization or oromucosal application, would likely offer safe and effective methods to investigate possible interactions and synergy.

Should positive outcomes result from such studies, phytopharmaceutical development may follow. The development of zero-cannabinoid cannabis chemotypes (de Meijer *et al.*, 2009b) has provided extracts that will facilitate discernment of the pharmacological effects and contributions of different fractions. Breeding work has already resulted in chemotypes that produce 97% of monoterpenoid content as myrcene, or 77% as limonene (E. de Meijer, pers. comm.). Selective cross-breeding of high-terpenoid- and high-phytocannabinoid-specific chemotypes has thus become a rational target that may lead to novel approaches to such disorders as treatment-resistant depression, anxiety, drug dependency, dementia and a panoply of dermatological disorders, as well as industrial applications as safer pesticides and antiseptics. A better future via cannabis phytochemistry may be an achievable goal through further research of the entourage effect in this versatile plant that may help it fulfil its promise as a pharmacological treasure trove.

Acknowledgements

The author offers appreciation to the following individuals, who provided materials and/or consultation: David Potter, Etienne de Meijer, John McPartland, David Watson, Rob Clarke, Indalecio Lozano, Tamas Bíró, José Crippa, Roger

Pertwee, Colin Stott, Vincenzo Di Marzo, Luciano De Petrocellis, Patrick McGovern, John Riddle and Elisaldo Carlini. Most of all, I would like to thank Raphael Mechoulam for his example, guidance, friendship, a life of good works and for listening to many 'crazy ideas'.

Conflict of Interest

The author is a Senior Medical Advisor to GW Pharmaceuticals and serves as a consultant.

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Patient-Reported Symptom Relief Following Medical Cannabis Consumption

Sarah S. Stith¹, Jacob M. Vigil^{2*}, Franco Brockelman³, Keenan Keeling³ and Branden Hall³

¹ Department of Economics, The University of New Mexico, Albuquerque, NM, United States, ² Department of Psychology, The University of New Mexico, Albuquerque, NM, United States, ³ The MoreBetter Ltd., Washington, DC, United States

OPEN ACCESS

Edited by:

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*Correspondence:

Jacob M. Vigil
vigilj@unm.edu

Specialty section:

This article was submitted to
Ethnopharmacology,
a section of the journal
Frontiers in Pharmacology

Received: 11 April 2018

Accepted: 26 July 2018

Published: 28 August 2018

Citation:

Stith SS, Vigil JM, Brockelman F,
Keeling K and Hall B (2018)
Patient-Reported Symptom Relief
Following Medical Cannabis
Consumption.
Front. Pharmacol. 9:916.
doi: 10.3389/fphar.2018.00916

Background: The Releaf App™ mobile software application (app) data was used to measure self-reported effectiveness and side effects of medical cannabis used under naturalistic conditions.

Methods: Between 5/03/2016 and 12/16/2017, 2,830 Releaf App™ users completed 13,638 individual sessions self-administering medical cannabis and indicated their primary health symptom severity rating on an 11-point (0–10) visual analog scale in real-time prior to and following cannabis consumption, along with experienced side effects.

Results: Releaf App™ responders used cannabis to treat myriad health symptoms, the most frequent relating to pain, anxiety, and depressive conditions. Significant symptom severity reductions were reported for all the symptom categories, with mean reductions between 2.8 and 4.6 points (ds ranged from 1.29–2.39, $ps < 0.001$). On average, higher pre-dosing symptom levels were associated with greater reported symptom relief, and users treating anxiety or depression-related symptoms reported significantly more relief ($ps < 0.001$) than users with pain symptoms. Of the 42 possible side effects, users were more likely to indicate and showed a stronger correlation between symptom relief and experiences of positive (94% of sessions) or a context-specific side effects (76%), whereas negative side effects (60%) were associated with lessened, yet still significant symptom relief and were more common among patients treating a depressive symptom relative to patients treating anxiety and pain-related conditions.

Conclusion: Patient-managed cannabis use is associated with clinically significant improvements in self-reported symptom relief for treating a wide range of health conditions, along with frequent positive and negative side effects.

Keywords: pain, anxiety, depression, cannabis, marijuana, quality of life, symptom management, side effects

INTRODUCTION

Medicinal cannabis use is expanding rapidly in the United States, with thousands of new users daily, particularly older patients and people with significant health concerns, treating many different symptoms (Centers for Disease Control and Prevention, 2016; Han et al., 2016). Most patients have a wide variety of medicinal cannabis products available to them, ranging from traditional flower to edibles and tinctures. Naturalistic observational studies are generally well-suited for capturing how patients manage their treatment decisions in real-life, and how patient-managed cannabis therapies may contribute to symptom relief and potential side effects from use. Observational research designs allow patients to use the myriad *Cannabis* strains and cannabis-derived formulations (e.g., concentrates, tinctures, edibles, topicals, suppositories, toothpaste) made at home and/or commercially available and widely used in society, and can incorporate the breadth of health conditions for which medical cannabis has been sanctioned for use at the state-level. Lastly, observational studies also circumvent research barriers associated with cannabis' Schedule I status under United States federal law, which makes randomized controlled trials (RCTs) challenging to conduct (Stith and Vigil, 2016; National Academies of Sciences, Engineering, and Medicine, 2017).

Since its release in 2016, the commercially developed Releaf App™ application (app; Releaf App, 2018) has been the only publically available, incentive-free patient educational software program designed for recording how individual cannabis usage sessions may correspond to immediate changes in primary symptom intensity levels and experienced side effects. This electronic assessment tool enables patients to monitor and manage their cannabis consumption decisions under naturalistic conditions while avoiding the limitations of retrospective survey collection methods (e.g., memory bias, social desirability effects). We used the Releaf App™ repository of over 2,830 patients and 13,368 individual cannabis administration sessions to examine two research questions: How does cannabis used under naturalistic conditions affect user-experienced symptom relief and side effects? Does the magnitude of experienced symptom relief and the prevalence of side effects vary across symptom categories? The results have clinical relevance for understanding how patient-managed medical cannabis therapies may correspond to changes in symptom intensity and potential side effects among people using cannabis for treating distinct health conditions (Hill and Weiss, 2016; Rubin, 2017).

MATERIALS AND METHODS

Study Design

A naturalistic observational research design, approved by the Institutional Review Board at the University of New Mexico, was used to analyze the Releaf App™ user-submitted data recorded between 5/03/2016 and 12/16/2017. Releaf App™ is a cross-platform (iOS and Android) mobile and tablet app backed by a secure cloud programming interface for capturing, processing, and storing anonymized user data. Out of 4,369 total

users and 23,373 user interactions, we included only cannabis consumption sessions with reported starting symptom levels greater than 0 (on a 0–10, 11-point scale) and ending symptom levels reported within 90 min of the start of the session, resulting in a final sample of 2,830 users and 13,638 individual sessions for analysis. The Releaf App™ measures 27 possible negative symptom categories and 42 possible side effects. Symptoms were ultimately derived from qualifying conditions across medical cannabis programs in the United States, along with a few suggested by dispensaries and patients. The side effects (called “feelings” within the app) were crowd-sourced among Releaf App™ developers, beta testers, dispensaries, and patients, and included 19 positive, 12 negative, and 11 context-specific side effects available for selection. **Supplementary Tables S1, S2** in the **Supplemental Appendix** provide descriptive statistics for all symptoms and side effects.

User sessions consist of a series of electronic instructions for recording characteristics of the cannabis medication (e.g., strain, potency, formulation), pre-dosing symptom severity rating along an 11-point visual analog facial pain scale from 0 (no detectable symptom level) to 10 (severe), the timing of cannabis consumption, a post-dosing symptom severity rating, and the option to indicate any of the 42 listed side effects at any time during the session. Among our primary sample of users, 2,332 users reported side effects during 10,535 sessions.

Study Outcomes

Our goal was to calculate changes in patient-perceived symptom severity, the prevalence of positive and negative side effects associated with cannabis consumption, and whether the reported-effects differs depending on the symptom for which users were seeking treatment. We measured changes in symptom relief by subtracting the ending symptom level from the beginning symptom (possible range from –10 to 10). (**Supplementary Figure S1** in the **Supplemental Appendix** provides a frequency table for each level of symptom relief.) Side effects were recorded as {0,1} variables for whether the user selected that side effect from the menu. We categorize the side effects as positive, negative, or context-specific and then convert these categories of side effects into {0,1} outcomes, count outcomes and outcomes measuring the portion of total available side effects in that category a user selected.

Statistical Analysis

We use means comparisons and least squares regression models to estimate the absolute and relative symptom changes and side effect profiles resulting from the cannabis user sessions. We also created an *adjusted symptom relief profile score*, the mean change in symptom levels plus the absolute number of listed negative side effects, to provide a relative metric of cost-benefit tradeoffs associated with cannabis use. Due to the small user counts for some of the reported symptoms, the large number of possible symptoms, and to facilitate interpretation in our regression analysis, we aggregate the most commonly reported symptoms across three broad symptom categories that included: Anxiety Symptoms (agitation/irritability, anxiety, insomnia, stress, and muscle spasms), Pain Symptoms (ten pain categories), and

Depression Symptoms (depression). The remaining types of symptoms are less frequently reported or not clearly categorized. We also report the full regression results for the three categories of side effects (positive, negative, and context-specific) and the sign for regressions of symptom relief on the full range of 42 side effects. Standard errors are clustered at the user level to control for heteroskedasticity and arbitrary correlation.

RESULTS

Figure 1 shows the starting and ending symptom severity levels, the change in levels, the Cohen's d of the difference, and the adjusted symptom relief profile score for each of the 27 discrete symptom categories. For all symptoms, the null hypothesis that the starting symptom severity level is less than or equal to the ending symptom severity can be rejected at the $p < 0.001$ level. Using the adjusted symptom relief measure (symptom relief plus negative side effects), all but users with convulsions, dizziness, excessive appetite, or tremors experienced a net improvement in their symptom severity levels. Even for these symptoms, the adjusted mean symptom relief score still indicates a net benefit from use and the lack of a statistically significant change likely relates more to the small number of observations rather than the lack of an effect, given that these symptoms together constituted less than 3% of users and less than 1% of our sample. For all other symptoms, the null hypothesis of an increase or no change in the adjusted symptom relief score can be rejected at the $p < 0.001$ level.

Table 1 provides additional information on starting and ending symptom severity levels, mean symptom relief, and

the prevalence of positive, negative, and context-specific side effects by the aggregated symptom categories (anxiety, pain, and depression symptoms). For completeness, we include a fifth column including the remaining discrete symptom categories which did not fall under the three aggregated symptom categories. Little variation exists in starting and ending symptom levels and the symptom relief experienced, with the average user reporting a symptom decrease of 3.7. With regards to side effects, those with depression have a higher probability of reporting negative or context-specific side effects. The most common positive side effects are “relaxed” (64%), “peaceful” (54%), and “comfy” (38%), the most common negative side effects are “dry mouth” (23%), “foggy” (22%), and “forgetful” (13%) and the most common context-specific side effects are “high” (32%), “sleepy” (27%), and “thirsty” (27%).

Table 2 examines how symptom relief varies across the broader symptom categories, with the constant representing the mean adjusted symptom change for the omitted category, (patients with pain-related symptoms). The first two regressions shown in **Table 2** indicate that people with anxiety and depression report greater relief from using cannabis than people with chronic pain, and users with higher starting symptom levels report greater symptom relief. (The effects of cannabis on anxiety and depression symptoms are not statistically different from each other, although they are both greater than the effect of cannabis on pain-related symptoms). Negative responses or increases in symptom severity do occur, but the intercept in combination with the starting symptom level predicts that increases in symptom severity levels predominantly occur among users with starting symptoms equal to one. The third column in **Table 2** shows that cannabis is more effective for anxiety and depression symptoms than for pain-related symptoms among patients reporting higher

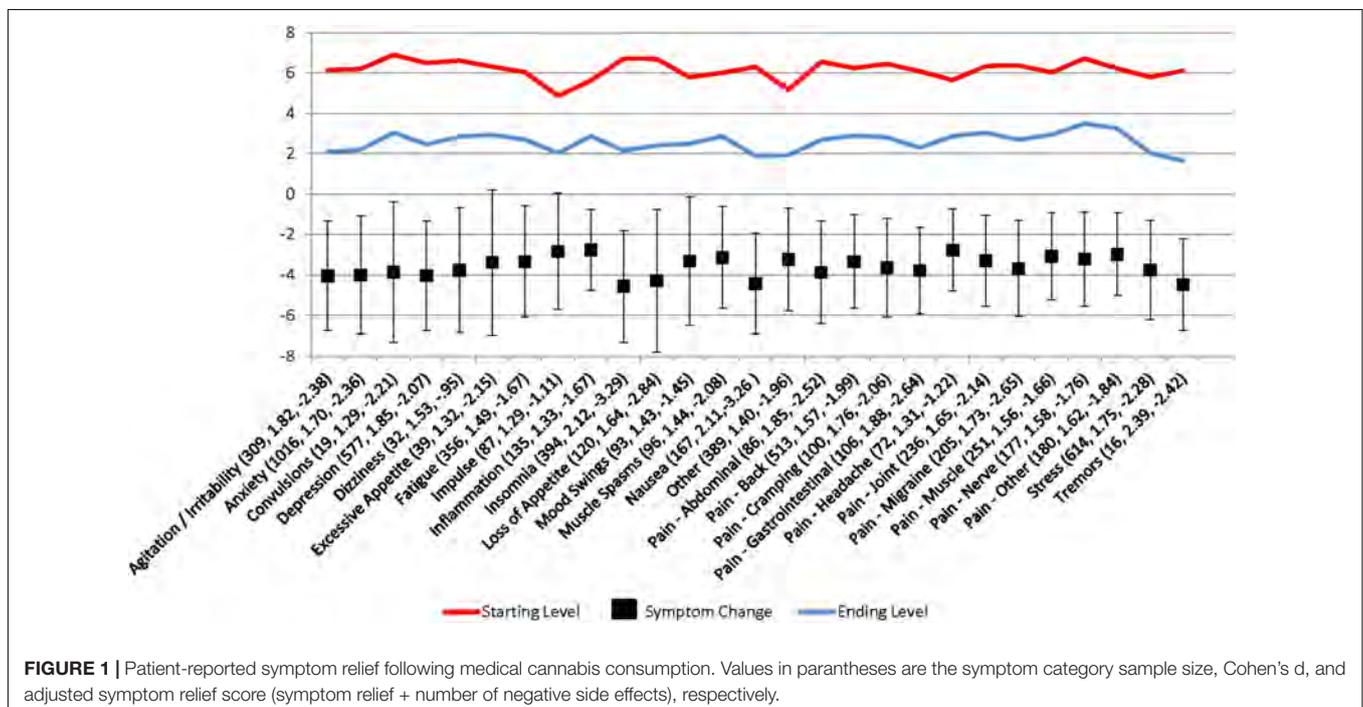


TABLE 1 | Descriptive statistics – symptom levels and experienced side effects.

	Overall	Anxiety symptoms	Pain symptoms	Depression symptoms	Other
N Sessions	13638	5343	4267	1440	2588
N Users	2830	1679	1223	577	1026
Starting symptom level	6.2 ± 2.2	6.2 ± 2.3	6.3 ± 2.0	6.5 ± 2.2	5.8 ± 2.4
Ending symptom level	2.5 ± 2.2	2.2 ± 2.2	3.0 ± 2.1	2.5 ± 2.2	2.4 ± 2.3
Symptom relief	-3.7 ± 2.6	-4.0 ± 2.8	-3.3 ± 2.3	-4.0 ± 2.7	-3.4 ± 2.8
Better	94.2%	94.8%	94.7%	95.4%	91.6%
Same	2.7%	2.4%	2.8%	2.4%	3.2%
Worse	3.1%	2.8%	2.5%	2.2%	5.2%
Any positive side effect	94.4%	94.7%	94.5%	93.9%	94.2%
Any negative side effect	60.0%	60.0%	58.9%	65.5%	58.8%
Any context-specific side effect	76.2%	75.2%	75.9%	80.1%	76.6%
# of positive side effects	4.6 ± 3.2	4.6 ± 3.2	4.4 ± 3.1	4.8 ± 3.4	4.8 ± 3.4
# of negative side effects	1.4 ± 1.7	1.4 ± 1.7	1.3 ± 1.6	1.6 ± 1.9	1.3 ± 1.7
# of context-specific side effects	2.0 ± 1.9	2.0 ± 1.9	1.9 ± 1.9	2.1 ± 1.9	2.0 ± 1.9
% of positive side effects	24%	24%	23%	26%	25%
% of negative side effects	11%	11%	10%	13%	10%
% of context-specific side effects	20%	20%	19%	21%	20%

Symptoms designated as treatable with benzodiazepines (Anxiety Symptoms) include agitation/irritability, anxiety, insomnia, muscle spasms, and stress. Symptoms associated with Opioid treatment (Pain Symptoms) include all ten pain conditions. Depression is the only symptom designated as treatable with antidepressants.

TABLE 2 | Reported symptom relief for users treating anxiety, pain, and depression.

	Outcome = symptom relief		
	(1)	(2)	(3)
Constant (opioid mean)	-3.309*** (-3.459 to -3.160)	1.120*** (0.804 to 1.436)	0.355** (0.034 to 0.675)
Anxiety symptoms	-0.704*** (-0.944 to -0.465)	-0.763*** (-0.953 to -0.574)	0.365* (-0.062 to 0.792)
Depression symptoms	-0.723*** (-1.060 to -0.385)	-0.563*** (-0.817 to -0.310)	0.643* (-0.021 to 1.308)
Starting symptom level (1–10)		-0.706*** (-0.757 to -0.656)	-0.582*** (-0.639 to -0.525)
Anxiety*start			-0.181*** (-0.259 to -0.102)
Depression*start			-0.189*** (-0.305 to -0.074)
Observations	11,050	11,050	11,050
R ²	0.018	0.372	0.377

Each column represents a separate regression. The omitted category is symptoms treatable with an opioid medication. Robust standard errors are clustered at the user level. The coefficients are reported in line with the variable names with confidence intervals below. Coefficients are reported with 95% Confidence Intervals below. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

symptom severity levels (A graphical representation of this relationship is presented in **Supplementary Figure S2** in the **Supplemental Appendix**).

In order to take advantage of the full range of symptom categories available to Releaf AppTM users, we also ran regressions including dummy variables for each of the symptoms, using back pain as the omitted category. After controlling for starting symptom level, clustering the standard errors at the user level, and using a statistical significance threshold of $p < 0.05$, our results indicate that patients report greater symptom relief for treating agitation/irritability, anxiety, depression, excessive

appetite, insomnia, loss of appetite, nausea, gastrointestinal pain, stress, and tremors than they do for treating back pain. Patients reported less symptom relief for treating impulsivity, headache, and nerve pain as compared to relief for treating back pain. The symptom relief for the other discrete symptom categories was indistinguishable from the reported symptom relief associated with back pain.

Table 3 explores whether patients using cannabis to treat pain, anxiety, or depressive symptoms differ in their experiences of positive, negative, or context-specific side effects. Chows tests (Chow, 1960) showed that users with anxiety-related symptoms

TABLE 3 | Differences in side effect profiles across symptom categories.

	Outcome = side effect type		
	Positive	Negative	Context-specific
		Any	
Constant (opioid mean)	0.966*** (0.942 to 0.989)	0.496*** (0.428 to 0.565)	0.695*** (0.637 to 0.753)
Anxiety symptoms	0.001 (-0.012 to 0.015)	0.013 (-0.033 to 0.059)	-0.006 (-0.049 to 0.037)
Depression symptoms	-0.006 (-0.029 to 0.017)	0.066** (0.002 to 0.131)	0.042* (-0.005 to 0.090)
Starting symptom level	-0.003* (-0.007 to 0.000)	0.015*** (0.007 to 0.024)	0.010** (0.002 to 0.019)
		Number	
Constant (opioid mean)	4.583*** (4.013 to 5.154)	1.081*** (0.768 to 1.395)	1.652*** (1.356 to 1.947)
Anxiety symptoms	0.182 (-0.100 to 0.465)	0.077 (-0.104 to 0.257)	0.077 (-0.113 to 0.268)
Depression symptoms	0.476* (-0.010 to 0.962)	0.324** (0.053 to 0.596)	0.134 (-0.187 to 0.454)
Starting symptom level	-0.035 (-0.142 to 0.072)	0.036** (0.000 to 0.072)	0.044** (0.003 to 0.085)
		Percent of possible	
Constant (opioid mean)	0.241*** (0.211 to 0.271)	0.083*** (0.059 to 0.107)	0.165*** (0.136 to 0.195)
Anxiety symptoms	0.01 (-0.005 to 0.024)	0.006 (-0.008 to 0.020)	0.008 (-0.011 to 0.027)
Depression symptoms	0.025* (-0.001 to 0.051)	0.025** (0.004 to 0.046)	0.013 (-0.019 to 0.045)
Starting symptom level	-0.002 (-0.007 to 0.004)	0.003** (0.000 to 0.006)	0.004** (0.000 to 0.009)

The first panel uses {0,1} outcomes for the presence of side effects in each category, the second uses the count of side effects reported by category, and the third uses the number of reported side effects for each category divided by the total number of possible side effects a user could select in that category. Robust standard errors are clustered at the user level. Coefficients are reported with 95% Confidence Intervals below. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

are no more or less likely than those with pain symptoms to report any of the three categories of side effects. Individuals with depression, however, are more likely to report negative and context-specific side effects than positive side effects. Higher starting symptom levels are also associated with more negative or context-specific side effect reporting and this relationship persists whether the side effect profile is defined as any of the side effects from that category of side effects, the number of side effects by category, or the percent of possible side effects in a category.

Table 4 tests whether different types of side effects are associated with differences in symptom relief. The results are robust across specifications; reporting positive or context-specific side effects is associated with greater symptom relief, while reporting negative side effects is associated with less symptom relief. For example, based on Column (4), a person with a starting symptom level of 5 who reports 100% of negative side effects would experience a 0.5 point increase in symptom severity on a 1–10 scale, whereas a similar user who does not report any negative side effects would experience 2.2 points of symptom

relief, highlighting the importance of adjusting for starting symptom severity level and side effect profiles when evaluating the overall effectiveness of cannabis as a treatment modality.

DISCUSSION

This is the largest observational study to measure immediate changes in patient-reported symptom severity ratings and experienced side effects in real-time from using cannabis under naturalistic conditions. Building on previous research showing that cannabis may be an effective substitute for opioids (Hurd, 2016; Vigil et al., 2017) and other classes of prescription medications (e.g., sedatives; Piper et al., 2017; Stith et al., 2017), we provide evidence that cannabis is used to treat many different types of symptoms for which conventional pharmaceutical medications are typically prescribed, and that the magnitude of reported symptom relief and side effect profiles from using cannabis varies for people with different symptoms.

TABLE 4 | Association of positive, negative, and context-specific side effects with symptom relief.

	Outcome = symptom relief			
	(1)	(2)	(3)	(4)
	Any {0,1}		Percent of possible in category	
Positive	−1.100*** (−1.360 to −0.841)	−1.344*** (−1.578 to −1.111)	−2.345*** (−3.046 to −1.643)	−2.899*** (−3.653 to −2.145)
Negative	0.174** (0.015 to 0.334)	0.336*** (0.192 to 0.480)	2.311*** (1.461 to 3.161)	2.772*** (2.045 to 3.498)
Context-specific	−0.339*** (−0.540 to −0.138)	−0.239*** (−0.413 to −0.065)	−0.781** (−1.495 to −0.068)	−0.417 (−0.931 to 0.096)
Starting symptom level		−0.660*** (−0.710 to −0.610)		−0.666*** (−0.724 to −0.608)
Constant	−2.307*** (−2.625 to −1.989)	1.894*** (1.441 to 2.348)	−3.098*** (−3.372 to −2.824)	1.100*** (0.818 to 1.382)
Observations	10,535	10,535	10,535	10,535
R ²	0.015	0.349	0.036	0.376

The first two columns measure use the existence of each category of side effect as independent variables, while the second two columns use the percent of possible in each category of side effects. The second and fourth columns include the starting symptom level. In all four regressions, the outcome is the change in symptom severity. Robust standard errors are clustered at the user level. Coefficients are reported with 95% Confidence Intervals below. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

The Releaf App™ users consumed cannabis to treat a wide range of health symptoms, the most frequent relating to pain, anxiety, or depression. Clinically and statistically significant reductions in patient-reported symptom severity levels existed in every single symptom category, suggesting that cannabis may be an effective substitute for several classes of medications with potentially dangerous and uncomfortable side effects and risky polypharmaceutical interactions, including opioids, benzodiazepines, and antidepressants (Weich et al., 2014; Centers for Disease Control and Prevention, 2016; Fontanella et al., 2016; Rudd et al., 2016; Sharma et al., 2016). Higher pre-dosing symptom levels were generally associated with greater post-dosing symptom relief and users treating an anxiety-related symptom or depression showed stronger symptom relief than users treating a pain symptom, even though depression is not a condition approved for medical cannabis use in most states.

Similar to clinical reviews showing that cannabis is associated with numerous, yet generally non-serious side effects (Wang et al., 2008; Whiting et al., 2016), positive and context-specific side effects were more commonly reported than negative side effects by the Releaf App™ users, with the most frequent reported side effects being positive (relaxed, peaceful, comfy) and the least frequent side effects being negative (paranoid, confused, headache). Positive side effect reporting was associated with the greatest reported symptom relief, followed by context-specific side effects, while negative side effects were associated with lower reported symptom relief. In general, patients treating depression were more likely to indicate a negative side effect than patients treating anxiety- or pain-related symptoms, though even users who reported only negative side effects reported significant decreases in moderate to severe symptom intensity levels after using cannabis.

One of the most striking patterns in the current results was the breadth of symptoms that appeared to improve following

cannabis consumption. This pattern of responses could have been a function of characteristics of the software user interface (e.g., symptom intensity scale range), manner in which responders interacted with their mobile device (e.g., visual attention to common symptom severity levels), or with the systemic nature by which phytocannabinoids may affect the human mind and body. According to the endocannabinoid deficiency theory, many mental and physical health disturbances result from the dysregulation of the body's innate endocannabinoid system (ECS; Smith and Wagner, 2014; Di Marzo et al., 2015; Karhson et al., 2016; Russo, 2018), often described as a master network of chemical signals that promote somatic and psychological homeostasis, or psychobiological state-efficiency (Bermudez-Silva et al., 2010; Silvestri and Di Marzo, 2013; Acharya et al., 2017). The ECS consists of natural ligands (e.g., anandamide and 2-AG) and receptors (CB1 and CB2) that appear to play a major role in efficient regulation of a wide range of systems that include sleep, feeding (e.g., gut permeability and adipogenesis), libido and fertility, pain perception, motivation, happiness, anxiety, learning and memory, social functioning, autoimmune responses, cellular redox, and cancer pathophysiology (Valvassori et al., 2009; Muccioli et al., 2010; Abdel-Salam et al., 2012; Cani, 2012; Burstein, 2015; Du Plessis et al., 2015; McPartland et al., 2015; Karhson et al., 2016; Pava et al., 2016; Tegeder, 2016; Turcotte et al., 2016; Androvicova et al., 2017; Sierra et al., 2018). In other words, unlike conventional pharmaceutical approaches, which largely target specific neurotransmitter sites (e.g., monoamine neurotransmitter hypothesis; Delgado, 2000; Ng et al., 2015), cannabis may act to improve a broad spectrum of symptoms by regulating homeostatic functioning, perhaps best described as a system-modulating rather than symptom-modulating form of therapy.

Notwithstanding the strengths of the naturalistic research design and the potential implications of the study's findings,

the study was limited primarily by the lack of a control group, e.g., non-cannabis users with the same symptom using a mobile device to indicate their immediate symptom intensity levels. There is also the potential confound of user-selection bias and exclusion of users that failed to complete sessions or even use the Releaf App™ due to a lack of symptom relief or negative side effects. (It is possible that selection bias could have worked in the opposite way, excluding patients that are already satisfied with their cannabis choices and therefore choose not to use the software app). This study chose to focus on the existence of symptom relief and side effects rather than offer clinical guidance as to which cannabis products offer preferential symptom relief and side effects profiles. As such we did not include product characteristics, e.g., routes of administration, quantity and method of ingestion, and cannabinoid content, all of which are likely crucial for understanding how cannabis affects symptom relief and side effect manifestation. We only show that, on average, most cannabis users experience symptom relief. Future research will benefit by incorporating these contextual factors into measurements of patient decisions and by dissecting how fundamental characteristics of the cannabis products themselves affect immediate and longer term changes in symptom relief and potential adverse consequences.

Patients with certain health conditions such as neurological disorders (e.g., multiple sclerosis, seizures, epilepsy, headache) may face differential risks for experiencing adverse effects or exacerbating their symptoms, for instance, depending on the amount of delta-9-tetrahydrocannabinol they consume, and caution should be used for patients considering using highly potent cannabis products (Solimini et al., 2017). Complicating matters are the allogamous (variable) and unstable nature of the *Cannabis* plant and the inherent inconsistencies in the chemical contents across plant batches and derived formulations, which are affected by genetic characteristics, but also environmental, cultivation, and storage conditions (Thomas and Pollard, 2016; Pacifici et al., 2017, 2018). These factors present challenges for both medical cannabis consumers and researchers as patients never have continuous access to cannabis products with precisely consistent chemotypes. Cannabis-based products (e.g., dried

flower vs. oils) can differ in their dose reliability, and researchers have offered guidelines for dosing titration and experimental usage (Kahan et al., 2014; Pichini et al., 2018). However, until federal laws currently restricting pharmacodynamics research in the United States are reformed (Stith and Vigil, 2016) investigators still have tremendous opportunities to develop and incorporate innovative assessment tools, like the Releaf App™, into observational research designs for measuring how patients experience self-directed cannabis treatment in their normal everyday lives outside of clinical settings.

AUTHOR CONTRIBUTIONS

JV and SS conceived the study. FB, KK, and BH independently designed and developed the Releaf App™ and server infrastructure as part of their effort to help create an education tool for medical cannabis patients. SS conducted the analyses. JV and SS drafted the manuscript. All authors contributed substantially to its intellectual content and revision.

FUNDING

This research was supported in part by the University of New Mexico Medical Cannabis Research Fund (mcrf.unm.edu).

ACKNOWLEDGMENTS

All authors had access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2018.00916/full#supplementary-material>

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Conflict of Interest Statement: The authors FB, KK, and BH were employed by company MoreBetter Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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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

Published: 23 April 2009

Received: 3 December 2008

Substance Abuse Treatment, Prevention, and Policy 2009, **4**:7 doi:10.1186/1747-597X-4-7

Accepted: 23 April 2009

This article is available from: <http://www.substanceabusepolicy.com/content/4/1/7>

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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.

Acknowledgements

This study was made possible by grant funding from the Canadian Institutes of Health Research (CIHR) [Funding reference: MOP-77813] and career support provided by the CIHR to Dr. Johnson.

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SHEREEF M. ELNAHAL, MD, MBA
Commissioner

January 23, 2019

Re: REVISED Final Agency Decision: Petitions to Establish Additional Debilitating Medical Conditions under the New Jersey Medicinal Marijuana Program

Dear Petitioners:

On March 22, 2018, I issued a final agency decision in the matter of the Department of Health's (Department) Request for Petitions to establish additional deliberating medical conditions under the New Jersey Medicinal Marijuana Program (MMP). In this final decision, I added chronic pain related to a musculoskeletal disorder as a debilitating medical condition to the MMP. Included in this chronic pain category was opioid use disorder, for which the Department received a petition, because the withdrawal symptoms for this disorder can cause severe and agonizing pain and research evidences that the use of medical marijuana was not only an effective alternative treatment to the opioids that are commonly used to treat this disorder but also reduces the likelihood of a patient developing opioid use disorder. As explained in detail below, after further review of this petition against the opioid crisis that is plaguing our State and research suggesting that the use of medical marijuana in conjunction with medication-assisted therapy to treat this disorder may aid in the reduction of relapses and assist with the prevention of opioid overdose deaths, I am issuing this revised final decision to include opioid use disorder as a standalone deliberating medical condition under the MMP. With this decision, opioid use disorder patients are eligible for medical marijuana if they suffer from chronic, painful withdrawal symptoms or as an adjunct treatment to their current medication-assisted treatment regimen. Accordingly, this Revised Final Agency Decision replaces my March 22nd final agency decision.

This letter sets forth the basis, rationale and final decision in the matter of the Department of Health's (Department) Request for Petitions to establish additional deliberating medical conditions under the New Jersey Medicinal Marijuana Program (MMP). As explained in detail below, I am granting the petitions seeking to add chronic pain conditions that are related to musculoskeletal disorders, chronic pain conditions that are of a visceral origin, as well as Tourette's Syndrome, migraine, and anxiety as debilitating medical conditions under the MMP. Additionally, I am granting the petition seeking to add opioid use disorder to the MMP, with the condition that medical marijuana be prescribed in conjunction with medication-assisted therapy for the treatment of the disorder. However, I am denying the petitions seeking to add asthma and chronic fatigue syndrome to the MMP.

In reaching this decision, I considered the Request for Petitions, the petitions submitted in response to the Request, the MMP panel's recommendations, written and oral public comments

received regarding various petitions, as well as the requirements of the New Jersey Compassionate Use Medical Marijuana Act (the Act), N.J.S.A. 24:6I-1 et seq., and the regulations promulgated thereunder. The referenced materials are incorporated herein and made a part of this final decision.

The Request for Petitions

On July 5, 2016, the Department published the Request for Petitions in the New Jersey Register advising that from August 1, 2016 to August 31, 2016, it was accepting petitions to establish additional medical conditions as “debilitating” under the MMP. 48 N.J.R. 1395(a). The Request for Petitions stated that the Department was seeking petitions in accordance with the Act, which authorizes the Department to include additional debilitating medical conditions under the MMP.

In the Request for Petitions, the public was advised that submitted petitions were required to include the following information, pursuant to N.J.A.C. 8:64-5.3:

- (1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;
- (2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;
- (3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting, or otherwise severely impair the patient's ability to carry on activities of daily living;
- (4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;
- (5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and
- (6) Letters of support from physicians or other licensed health care professional knowledgeable about the condition.

The Department also crafted a Petition Form that petitioners could use for their submissions. The form detailed the above-listed criteria, which each petitioner needed to provide in order for his or her submission to be accepted and considered.

In addition to publishing the request for petitions in the New Jersey Register, the Department also posted it on its website.

Completeness Review

At the close of the petition submission period, the Department received sixty-eight petitions. Thereafter, the Department reviewed each petition to determine whether it contained the information that was required for it to be accepted for consideration. From its review, the

Department determined that twenty-three petitions did not meet the criteria for consideration.¹ Accordingly, the Department denied these petitions under separate cover on December 7, 2016, pursuant to N.J.A.C. 8:64-5.3(b). The remaining forty-five petitions met the criteria for consideration and were accepted.

Statutory and Regulatory Criteria

The Act charges the Department with the responsibility of administering the State's MMP, including establishing a registry of qualifying patients and primary care givers. To qualify as a MMP patient, an individual must suffer from one of the debilitating medical conditions set forth in the Act. The Act defines a "debilitating medical condition" as:

- (1) one of the following conditions, if resistant to conventional medical therapy: seizure disorder, including epilepsy; intractable skeletal muscular spasticity; post-traumatic stress disorder; or glaucoma;
- (2) one of the following conditions, if severe or chronic pain, severe nausea or vomiting, cachexia, or wasting syndrome results from the condition or treatment thereof: positive status for human immunodeficiency virus; acquired immune deficiency syndrome; or cancer;
- (3) amyotrophic lateral sclerosis, multiple sclerosis, terminal cancer, muscular dystrophy, or inflammatory bowel disease, including Crohn's disease; [or]
- (4) terminal illness, if the physician has determined a prognosis of less than 12 months of life.

[N.J.S.A. 24:6I-3.]

In addition to the conditions listed in the Act, the Legislature authorized the Department to establish additional medical conditions as debilitating under the MMP. Ibid. Consistent with its statutory authority, the Department promulgated rules that outline the process for expanding the list of medical conditions that qualify as "debilitating" under the MMP. See N.J.A.C. 8:64-1.1 et seq. Pursuant to these rules, I am required to take into consideration the following factors in order to determine whether a condition should be added to the MMP as a "debilitating" medical condition that is likely to benefit from the use of medical marijuana to treat or alleviate the debilitating effect of the condition:

- (1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;
- (2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;
- (3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or

¹ Legislation was enacted during the pendency of the petitions, which added post-traumatic stress disorder to the list of conditions that qualify as debilitating under the MMP. As a result, the petitions seeking to add this condition to the MMP were deemed moot and not forwarded to the Panel for consideration.

vomiting or otherwise severely impair the patient's ability to carry on activities of daily living;

(4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;

(5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and

(6) Letters of support from physicians or other licensed health care professionals knowledgeable about the condition.

[N.J.A.C. 8:64-5.3]

The MMP Review Panel Meetings, Public Comments and Panel Recommendations

On May 11, 2017, the MMP Review Panel, which is a panel assembled by the Department to review and make recommendations on petitions seeking to add conditions to the MMP, met to review and hear public comments on the forty-five accepted petitions. At the meeting, the Panel acknowledged that they reviewed the material submitted with the petitions and that they also conducted their own independent analysis and research for each condition. During the meeting, the Panel also advised that it grouped the petitioned conditions into seven categories, namely chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, anxiety, asthma and chronic fatigue. After offering a panel discussion on each condition and hearing public comments from two individuals, both of whom expressed support for the MMP, the Panel voted on each petition. Based upon a majority vote of the members who were present at the meeting, the Panel recommended that chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety be approved as debilitating conditions under the MMP and recommended denial of asthma and chronic fatigue.

After the meeting, the Chairman of the Panel reduced the Panel's initial recommendations to writing and submitted it to me for consideration. In the initial recommendation letter, the Panel advised that it was recommending that I add chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety to the MMP because these conditions are debilitating, and medicinal marijuana was more likely than not to have the potential to be beneficial to treat or alleviate the debilitation associated with each condition.

As for asthma and chronic fatigue, the Panel recommended that these conditions not be added to the MMP because medical marijuana was not likely to have the potential to be beneficial to treat or alleviate the debilitation associated with the conditions.

After receiving the Panel's initial recommendation letter, it was posted on the Department's website for a 60-day public comment period to provide the public with an opportunity to submit written comments on the recommendations. At the time the comment period closed, the Department received approximately sixty comments, which were generally supportive of the MMP.

During the 60-day comment period, the Department's MMP Review Panel also convened a public hearing on September 18, 2017, which provided the public with an additional opportunity to comment on the recommendations. During this public hearing, the Panel heard from seven individuals. The comments provided by the commenters did not express any disagreement with the Panel's recommendations.

Upon the conclusion of the public comment period, the Panel reconvened for a final meeting on the petitions. At the meeting, which was held on October 26, 2017, the Panel further deliberated its recommendations on the petitioned conditions, taking into consideration the petitions, information submitted with the petitions, public comments, the factors outlined in N.J.A.C. 8:64-5.3, each member's own research or that done by others, as well as each member's education and training, in order to determine whether any changes should be made to the Panel's initial recommendations. In so deliberating, the Panel discussed each condition in turn and permitted additional public comment on the conditions. Based upon the Panel's extensive and thorough discussions, the majority of the Panel members present at the meeting voted to uphold their initial recommendations on the conditions. As such, the Panel's initial recommendations converted to the Panel's final recommendations to the Commissioner, pursuant to N.J.A.C. 8:64-5.3(f).

Findings and Decisions on the Petitions

For the reasons that follow, I am granting the petitions seeking to add chronic pain that is related to musculoskeletal disorders, chronic pain conditions that are of a visceral origin, as well as Tourette's Syndrome, migraine, opioid use disorder and anxiety under the MMP and denying the petitions seeking to include asthma and chronic fatigue syndrome under the MMP. In reaching my decision, I considered the statutory and regulatory criteria articulated above, the Panel's recommendations and their supporting materials, the petitions with supporting information, public comments, emerging research on medical marijuana and the transcripts of the Panel's meetings, which provides the Panel members' detailed discussions on each condition.

Granted Petitions

Chronic Pain associated with a Musculoskeletal Disorder

Based upon my independent review of the petitions, I am granting those seeking to add chronic pain associated with a musculoskeletal disorder to the MMP.² In coming to this

² Thirty-five of the petitions received by the Department concern various forms of chronic pain. After reviewing these petitions, the Panel determined that they fell into two categories: chronic pain associated with a musculoskeletal disorder and chronic pain of a visceral origin. Based upon my review of this matter, I find that the Panel made the appropriate categorizations of these petitions. Thus, I agree with the Panel that the chronic pain conditions sought to be added to the MMP should be generally labeled as chronic pain associated with a musculoskeletal disorder and chronic pain of a visceral origin, rather than the unique, individual conditions set forth in each chronic pain petition. The list of petitions that fall into each category are set forth in the Panel's recommendation letter, which is incorporated herein by reference. The only exception I have to the bundling of these petitions into the two chronic pain categories is the petition seeking to add opioid use disorder to the MMP, which I find should be granted as both a standalone disorder and as a condition that falls under the category of chronic pain associated with a musculoskeletal disorder.

conclusion, I reviewed this condition against the six regulatory criteria cited above and found that it meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic pain associated with a musculoskeletal disorder is a valid condition. According to the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), chronic pain associated with a musculoskeletal disorder is pain that persists beyond the usual course of an acute condition, which is typically three months or more or past the time for normal healing, and includes injury and inflammatory conditions "that cause pain in the body's joints; ligaments; muscles; nerves; tendons; and structures that support the limbs, neck, and back."³ Moreover, as noted by the Panel, the World Health Organization's International Classification of Diseases, as clinically modified by the NCHS (ICD-10-CM), uses unique alphanumeric codes to identify known diseases and other health problems and lists multiple codes for chronic pain.⁴ Given the fact that chronic pain associated with a musculoskeletal disorder has a common medical definition and maintains several ICD-10-CM codes, which entities covered by the Health Insurance Portability and Accountability Act must use for processing claims pursuant to rules promulgated by the U.S. Department of Health and Human Services, I find that chronic pain associated with a musculoskeletal disorder is a valid condition recognized by the medical community. See 45 C.F.R. 162.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. As set forth in the petitions and acknowledged by the Panel, the generally accepted treatments for chronic pain associated with a musculoskeletal disorder are opioids and non-steroid anti-inflammatory drugs (NSAIDs), both of which can have significant side effects. I agree. According to the Centers for Disease Control and Prevention (CDC), NSAIDs, such as ibuprofen, are a common treatment for chronic pain associated with a musculoskeletal disorder.⁵ The CDC also recognizes opioids, such as oxycodone and hydrocodone, as a common and medically accepted treatment for chronic musculoskeletal pain.⁶ Thus, I find that the treatments for chronic pain, namely NSAIDs and opioids, are recognized and accepted by the medical community and relate to a patient's suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that chronic pain associated with a musculoskeletal disorder itself as well as the treatment for this condition cause severe suffering for patients inflicted with this condition. As the name suggests, a patient with chronic pain associated with a musculoskeletal disorder experiences just that - pain. Specifically, musculoskeletal chronic pain can cause widespread or localized pain that may worsen with movement, stiffness or achiness, fatigue, and/or muscle twitches.⁷ Thus, the condition itself is the main culprit for the suffering experienced by patients with this disorder. While

³See <https://www.cdc.gov/nchs/data/nhsr/nhsr098.pdf> (last visited March 13, 2018). See also <https://www.cdc.gov/drugoverdose/prescribing/guideline.html> (last visited March 13, 2018).

⁴ See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited March 13, 2018).

⁵ See https://www.cdc.gov/drugoverdose/pdf/nonopioid_treatments-a.pdf (last visited March 13, 2018).

⁶ See <https://www.cdc.gov/drugoverdose/opioids/index.html> (last visited March 13, 2018).

⁷ See <https://my.clevelandclinic.org/health/diseases/14526-musculoskeletal-pain> (last visited March 13, 2018).

chronic pain, in and of itself, causes extensive pain, the treatment for chronic pain associated with a musculoskeletal disorder can also cause significant suffering. Specifically, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness⁸. And, opioids can cause constipation, nausea, respiratory depression, dependency, opioid use disorder, sedation and dizziness.⁹ All of these side effects can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that musculoskeletal chronic pain as well as the therapies to treat this condition cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatments for chronic musculoskeletal pain that cause the patient suffering, namely NSAIDs and opioids, are essentially the most viable conventional medical therapies offered for this condition, which was noted by the Panel. As such, I find that there is an absence of effective alternative medical therapies to the conventional therapies currently prescribed for chronic musculoskeletal pain that cause patients to suffer.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is extensive research establishing that the use of medical cannabis can relieve the chronic pain associated with a musculoskeletal disorder. Specifically, there are several peer-reviewed publications in leading medical journals, including a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, as well as a significant number of clinical trials, which found that the use of medical marijuana was effective in relieving chronic pain.¹⁰ As such, I find that there is general acceptance in the medical community that medicinal cannabis can alleviate the suffering caused by chronic musculoskeletal pain.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic musculoskeletal pain under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of chronic pain related to a musculoskeletal disorder is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that chronic pain related to a musculoskeletal disorder should be added to the MMP.

Chronic Pain Conditions of a Visceral Origin

From my detailed review of the petitions, I am granting those seeking to add chronic pain conditions of a visceral origin to the MMP. In coming to this conclusion, I reviewed the petitions

⁸ See <https://my.clevelandclinic.org/health/drugs/11086-non-steroidal-anti-inflammatory-medicines-nsaids> (last visited March 13, 2018).

⁹ See Footnote 6.

¹⁰ See, e.g., The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research, National Academies Press (2017) (<http://nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx>) (last visited March 13, 2018); Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials, British Journal of Clinical Pharmacology (2001) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243008/>) (last visited March 13, 2018).

against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

For the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic pain of a visceral origin is a valid condition. Chronic pain of a visceral origin is commonly defined by the medical community as pain that arises from the internal organs of the body and persists beyond the usual course of an acute condition, which is typically three months or more or past the time for normal healing.¹¹ Specifically, visceral pain is pain that results from the activation of nociceptors located in most viscera (internal organs of the body, specifically those within the chest (as the heart or lungs) or abdomen (as the liver, pancreas or intestines)) and the surrounding connective tissue.¹² Moreover, as noted by the Panel, there are multiple ICD-10-CM codes for chronic pain of a visceral origin, such as codes for pancreatitis, pain related to neurogenic bladder and bowel dysfunction, and irritable bowel syndrome. Because there is a common medical definition for chronic visceral pain as well as many ICD-10-CM codes for this condition, I find that chronic pain of a visceral origin is a valid and recognized medical condition.

As for the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. Like chronic musculoskeletal pain, chronic pain of a visceral origin is generally treated with opioids and NSAIDs, which, as I stated above, can have severe side effects. Indeed, the CDC advises that NSAIDs and opioids are the most common forms of treatment for chronic pain.¹³ Thus, I find that the treatments for chronic pain, namely NSAIDs and opioids, are recognized and accepted by the medical community as the treatments for chronic visceral pain and relate to a patient's suffering.

Regarding the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the chronic pain condition itself as well as the treatments for this condition cause severe suffering for patients stuck with this disorder. Specifically, visceral pain due to an obstruction of a hollow organ is poorly localized, deep, and cramping and may be referred to remote cutaneous sites.¹⁴ Visceral pain that is caused by an injury of organ capsules or other deep connective tissues may be more localized and sharp.¹⁵ As such, the actual condition is the main cause for the suffering experienced by patients with this disorder. Although chronic pain itself causes severe pain, the treatment for this condition can also result in significant suffering. As I outlined above, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness. And, opioids can cause constipation, nausea, respiratory depression, dependency, opioid use disorder, sedation and dizziness. So, the condition itself as well as the side effects from the medications used to treat this condition can prevent a patient from engaging

¹¹ See <https://medical-dictionary.thefreedictionary.com/visceral+pain> (last visited March 13, 2018).

¹² See <https://www.merckmanuals.com/professional/neurologic-disorders/pain/overview-of-pain> (last visited March 13, 2018).

¹³ See footnotes 5 and 6.

¹⁴ See footnote 12.

¹⁵ Ibid.

in activities of daily living and eviscerate one's quality of life. Accordingly, I find that both the condition of chronic pain as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatments for chronic pain that cause the patient suffering, which are NSAIDs and opioids, are the only viable conventional medical therapies offered for this condition.¹⁶ Therefore, I find that there is a lack of medically-accepted, alternative medical treatments to the conventional therapies currently recommended for chronic pain of this nature.

As for the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, the Panel concluded that there is comprehensive research demonstrating that the use of medicinal cannabis can alleviate the pain associated with chronic pain. As stated above, there are peer-reviewed publications in leading medical journals, including a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, and a number of clinical trials that found that the use of medical marijuana was effective in relieving chronic pain. As such, I find that the medical community has generally accepted the use of medicinal marijuana as a likely effective treatment for alleviating the suffering caused by chronic pain.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic visceral pain under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of chronic pain of a visceral origin is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that chronic pain of a visceral origin should be added to the MMP.

Tourette's Syndrome

After a careful review of the petition seeking to add Tourette's Syndrome (TS) to the MMP, I have decided to grant this petition. In formulating this determination, I reviewed the condition against the six regulatory criteria cited above and found that it meets the requirements for inclusion in the MMP.

Under the first factor, I must determine whether the condition is generally accepted in the medical community as a valid medical condition. I find that TS meets this requirement. Specifically, TS is commonly defined by the medical community as a neurological disorder characterized by repeated involuntary movements (motor tics) and uncontrollable vocal sounds (vocal tics), with symptoms usually manifesting before the age of eighteen.¹⁷ Moreover, a CDC study found that "1 of every 360 (0.3%) children 6 – 17 years of age in the United States have been diagnosed with TS based on parent[al] report[s]," with boys being "three to five times more

¹⁶ Ibid.

¹⁷ See <http://www.merckmanuals.com/professional/pediatrics/neurologic-disorders-in-children/tic-disorders-and-tourette-syndrome-in-children-and-adolescents> (last visited March 13, 2018).

likely to have TS than girls.”¹⁸ Accordingly, I find that TS is a valid and recognized medical condition.

Regarding the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. According to the petition and as acknowledged by the Panel, the generally accepted treatments for TS are medication and behavioral treatments, which can help manage the tics.¹⁹ As noted by the Panel, there is no one primary medication to treat TS and, as a result, there is a varying approach to how it is addressed.²⁰ Most medications prescribed for TS have not been approved by the U.S. Food and Drug Administration (FDA) for treating tics and the medications that are approved fall into the category of anti-psychotics, which can have serious adverse side effects that include weight gain, stiff muscles, tiredness, restlessness, and social withdrawal.²¹ As such, I find that the treatments for the symptoms of TS are recognized and accepted by the medical community as the treatments for this condition and relate to a patient's suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both TS itself as well as co-occurring conditions and the treatments for this condition cause severe suffering for patients inflicted with this condition. While the tics caused by TS clearly impair a patient's ability to carry on his or her activities of daily living, the co-occurring conditions that arise with this disorder can be equally if not more devastating to the patient. According to the National Institute of Neurological Disorders and Stroke, many individuals with TS experience additional neurobehavioral problems that often cause more impairment than the tics themselves. These include inattention, hyperactivity and impulsivity (attention deficit hyperactivity disorder — ADHD), problems with reading, writing, and arithmetic, and obsessive-compulsive symptoms such as intrusive thoughts/worries and repetitive behaviors.²² Thus, TS itself along with its co-occurring conditions negatively impact a patient's quality of life. Additionally, as I noted above, the pharmacological treatments for TS can cause serious side effects that negatively impact an individual's quality of life. As recognized by the Panel, TS is difficult to treat and very debilitating.²³ I concur. As such, I find that both the condition of TS as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must analyze the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the only FDA-approved therapies for TS are anti-psychotic medications. While these medications have an 80% rate of tic suppression, which was noted by the Panel, the medications have serious side effects that can include weight gain and social withdraw. And, although behavioral therapy is a treatment that teaches people with TS

¹⁸See <https://www.cdc.gov/ncbddd/tourette/data.html> (last visited March 13, 2018).

¹⁹ See <https://www.cdc.gov/ncbddd/tourette/treatments.html> (last visited March 13, 2018).

²⁰ In Re: Medicinal Marijuana Review Panel Transcript. 55: 4 -6. October 25, 2017.

²¹ See footnote 19.

²² <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Tourette-Syndrome-Fact-Sheet> (last visited March 13, 2018).

²³ In Re: Medicinal Marijuana Review Panel Transcript. 54:11. October 25, 2017.

ways to manage their tics, it is not a cure for tics. As such, the conventional therapies for TS, which are pharmaceutical and behavioral treatment, may not fully suppress or manage tics and the presence of TS may severely impair the patient's ability to carry on activities of daily living. Accordingly, I find that there is a lack of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for TS that cause suffering for some patients.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is research establishing that the use of medical cannabis can relieve the symptoms associated with TS. Evidence on the use of cannabis for effective symptomatic treatment of movement disorders, including TS, dates to the late 1990s with the work of Dr. Kirsten Müller-Vahl of the Hannover Medical School in Hannover, Germany.²⁴ Dr. Müller-Vahl's studies demonstrated improvements in global functioning and tic severity scores with cannabis use. Specifically, Dr. Müller-Vahl conducted a clinical survey among sixty-four TS patients of whom seventeen had reportedly consumed cannabis and approximately 82% of these patients reported a reduction in symptoms.²⁵ Subsequent studies of single cases confirmed that administration of 10mg of tetrahydrocannabinol (THC), which is one of the active chemical compounds in cannabis, led to an 80% reduction in tics and a simultaneous increase in the attention of patients.²⁶ And, a randomized, placebo-controlled six-week trial of up to 10mg THC per day confirmed the previous findings.²⁷ Furthermore, 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.²⁸ Moreover, several states, such as Minnesota and Illinois, have approved medical marijuana specifically for the treatment of TS. Even more, a recent systematic review and meta-analysis published in the Journal of the American Medical Association (JAMA) in 2015 suggests there is some evidence that cannabinoids may improve symptoms of TS.²⁹ While the 2015 JAMA review suggests that marijuana may only have a minimal effect on relieving the symptoms of TS, the fact that the study evidenced some relief, even with the limited number of clinical trials available on the medical benefits of marijuana due to the legal restrictions surrounding cannabis, shows promise that marijuana is effective for this condition. As such, I find that the totality of the above research exhibits a general consensus in the medical community that marijuana is likely to alleviate some of the suffering caused by TS.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of TS under the MMP, I find that the petition was submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of TS is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the

²⁴ Müller-Vahl, K R., et al. "Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol." *American Journal of Psychiatry* 156.3 (1999): 495-495 .

²⁵ See <http://researchfeatures.com/2017/06/01/cannabis-based-medication-tourettes-syndrome/> (last visited March 13, 2018).

²⁶ *Ibid.*

²⁷ *Ibid.*

²⁸ See <https://www.nap.edu/read/24625/chapter/6?term=tourette#104> (last visited March 13, 2018).

²⁹ See <https://media.jamanetwork.com/news-item/mixed-findings-regarding-quality-of-evidence-supporting-benefit-of-medical-marijuana/> (last visited March 13, 2018).

debilitating effect of this condition. As such, I find that Tourette's Syndrome should be added to the MMP.

Migraine

After a thorough review of the petitions, I am granting those seeking to add migraine to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that migraine meets this criterion. According to the Merck Manual, migraine is an episodic primary headache disorder.³⁰ Symptoms typically last four to seventy-two hours and may be severe.³¹ Pain is often unilateral, throbbing, worsen with exertion, and accompanied by symptoms such as nausea and sensitivity to light, sound, or odors. Auras occur in about 25% of patients, usually just before but sometimes after the headache.³² And, there are approximately 28 million individuals living with migraines in the United States.³³ As such, I find that migraine is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. As stated in the petitions and recognized by the Panel, the generally accepted treatments for migraines are NSAIDs, triptans, opioids and/or ergots (ergot alkaloids), all of which can have significant side effects.³⁴ Specifically, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness.³⁵ Side effects of triptans include nausea, dizziness, drowsiness and muscle weakness.³⁶ Furthermore, triptans should not be used by those who have a past history of, or risk factors, for heart disease, high blood pressure, high cholesterol, angina, peripheral vascular disease, impaired liver function, stroke or diabetes.³⁷ Ergots may worsen nausea and vomiting related to migraines, and it may also lead to medication-overuse headaches.³⁸ And, as outlined above, opioids have serious side effects including addiction and nausea.³⁹ Thus, I find that the treatments for migraine, namely NSAIDs, triptans, opioids and ergots, can cause a patient to suffer and are accepted by the medical community as the treatments for this condition.

³⁰ See <http://www.merckmanuals.com/professional/neurologic-disorders/headache/migraine> (last visited March 13, 2018).

³¹ *Ibid.*

³² *Ibid.*

³³ <https://www.hopkinsmedicine.org/otolaryngology/docs/Migraine%20patient%20handout.pdf> (last visited March 13, 2018).

³⁴ <https://www.hopkinsmedicine.org/otolaryngology/docs/Migraine%20patient%20handout.pdf> (last visited March 13, 2018). See also <https://www.mayoclinic.org/diseases-conditions/migraine-headache/diagnosis-treatment/drc-20360207> (last visited March 13, 2018).

³⁵ See <https://my.clevelandclinic.org/health/drugs/11086-non-steroidal-anti-inflammatory-medicines-nsaids> (last visited March 13, 2018).

³⁶ See <http://www.headaches.org/2007/10/25/triptans/> (last visited March 13, 2018).

³⁷ *Ibid.*

³⁸ See <https://www.drugs.com/mcd/migraine> (last visited March 13, 2018).

³⁹ See footnote 6.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the migraine condition itself as well as the treatments for this condition cause severe suffering for patients. As stated above, the condition itself causes intense pain, nausea and sensitivity to light, sound, or odors. In fact, the pain and sensitivity may become so intense that the patient may have no other option than to rest in a dark, quiet room until the migraine passes.⁴⁰ Thus, the migraine condition causes severe suffering.

The same holds true for migraine treatments. The side effects caused by the treatments for migraines can be equally if not worse than the symptoms produced by this condition. Specifically, the treatments, which include opioids and triptans, can cause nausea, dizziness, and muscle weakness and may even cause rebound symptoms that are more intense than the original onset of the migraine.⁴¹ Thus, the migraine condition as well as side effects accompanying the treatment for this condition impair or even prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. With this, I find not only that the migraine condition in and of itself causes a patient severe suffering but that the therapies to treat it also cause significant suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. The treatments for migraine that cause the patient suffering, namely NSAIDs, triptans, opioids and ergots, are the conventional medical therapies offered for this condition. Furthermore, as noted by the Panel, the conventional therapies are ineffective for some patients, leaving them with a decreased ability to function and a decreased quality of life. Alternatives such as biofeedback, ice packs, acupuncture, aromatherapy, adequate sleep, smoking cessation, avoiding any food and environmental triggers are available and may alleviate migraine symptoms.⁴² However, these alternative treatments usually do not treat all of the symptoms associated with a migraine and do not necessarily alleviate the patient's suffering caused by the migraine. Therefore, patients that are not responsive to conventional or alternative therapies may suffer constant unrelenting pain, which produces mental and physical debilitation. As such, I find that there are serious limitations with the medically-accepted, alternative medical therapies and the conventional therapies currently prescribed for migraine.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is extensive research establishing that the use of medical cannabis can relieve the pain associated with migraine. There are studies which found that the use of medical marijuana was effective in decreasing the frequency of migraine headaches and relieving migraine pain.⁴³ Most notably, a recent study recommended that prospective studies

⁴⁰ <https://www.hopkinsmedicine.org/otolaryngology/docs/Migraine%20patient%20handout.pdf> (last visited March 13, 2018).

⁴¹ *Ibid.*

⁴² *Ibid.* See also <https://migraine.com/complimentary-and-alternative-therapies/> (last visited March 13, 2018).

⁴³ Ethan B. Russo, Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes, *Cannabis and Cannabinoid Research*, 20a6, 1,1, 154. See <https://www.liebertpub.com/doi/10.1089/can.2016.0009> (last visited March 13, 2018).

should be conducted to explore a cause-and-effect relationship and the use of different strains, formulations, and doses of marijuana to better understand the effects of medical marijuana on migraine headache treatment and prophylaxis.⁴⁴ A majority of the Panel agreed that a review of the literature suggests that marijuana might alleviate some of the symptoms caused by a migraine with less side effects than commonly accepted medical treatment. Based upon this research, I find that there is generally accepted evidence in the medical community that medicinal cannabis can alleviate the suffering caused by migraine.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of migraine under the MMP, I find that the petitions were submitted with support from physicians and an advanced practice nurse. Indeed, one petition was submitted by a board certified anesthesiologist. Thus, I find that this requirement is met.

Based upon the above analysis, I find that the condition of migraine is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that migraine should be added to the MMP.

Anxiety

Based upon my independent review of the petitions, I am granting those seeking to add anxiety to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that anxiety satisfies this criteria. Specifically, the American Psychiatric Association defines anxiety and anxiety disorders as conditions characterized by excessive fear and behavioral disturbances.⁴⁵ Anxiety results from anticipation of a future threat and may be associated with symptoms of muscle tension, vigilance in preparation for future danger, and overly cautious or avoidant behaviors.⁴⁶ Additionally, there are multiple ICD-10-CM codes for anxiety disorders.⁴⁷ Because anxiety maintains a common definition in the medical community and has ICD-10-CM codes, I find that anxiety is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient’s suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. From my review of this condition, the generally accepted treatments for anxiety are dependent on the symptoms and the severity of the particular disorder. Mild and moderate forms of anxiety may not require a pharmacologic intervention, but may necessitate other forms of treatment, such as meditation, mindfulness, breathing techniques as well as psychotherapy (counseling) or cognitive therapy.⁴⁸ The most common classes of

⁴⁴ See <https://www.ncbi.nlm.nih.gov/pubmed/26749285> (last visited March 13, 2018).

⁴⁵ See <https://dsm.psychiatryonline.org/doi/abs/10.1176/appi.books.9780890425596.dsm05> (last visited March 13, 2018).

⁴⁶ *Ibid.*

⁴⁷ See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited March 13, 2018).

⁴⁸ See <https://adaa.org/finding-help/treatment#> (last visited March 14, 2018).

medications used to combat anxiety disorders are antidepressants, anti-anxiety drugs, and beta-blockers.⁴⁹ Antidepressants are safe and effective but they may be risky for children, teens, and young adults.⁵⁰ Antidepressants also come with a “black box” warning – the FDA’s strongest warning - advising that some people may have suicidal thoughts or make suicide attempts while taking the medication.⁵¹ The most common anti-anxiety medications are called benzodiazepines. As noted by the Panel, the common side effects of benzodiazepines include headache, confusion, tiredness, and in some cases nightmares and memory impairments.⁵² And, benzodiazepines carry a risk of dependence and addiction.⁵³ Furthermore, the FDA notes that the number of patients who were prescribed both an opioid analgesic and benzodiazepine increased by 41% between 2002 and 2014.⁵⁴ As a result, the FDA requires black box warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines to inform the patient about the serious risks associated with using these medications at the same time.⁵⁵ Thus, I find that the treatments for anxiety are recognized and accepted by the medical community as the treatments for this condition and relate to the suffering of the patient.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the anxiety condition itself as well as the treatments for this condition cause severe suffering for patients. Specifically, anxiety may lead to problems that negatively impact an individual's activities of daily living and quality of life and may lead to suicide and depression. Anxiety disorders can also cause significant distress or interfere with social, occupational, and other areas of functioning. In fact, an estimated 31.1% of U.S. adults experience an anxiety disorder at some time in their lives.⁵⁶ Medications, in some instances, may exacerbate the symptoms and are associated with debilitating side effects that can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that both the condition of anxiety as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. As discussed above, mild and moderate forms of anxiety may be treated with meditation, mindfulness, breathing techniques as well as counseling or cognitive therapy that can be effective. Progression to medication therapy may be initiated; however, in both instances, one must consider the therapeutic response. Failure to respond to therapies or side effects associated with treatments may result in significant impacts on quality of life. As such,

⁴⁹ *Ibid.*

⁵⁰ See <https://www.mayoclinic.org/diseases-conditions/teen-depression/in-depth/antidepressants/art-20047502> (last visited March 14, 2018).

⁵¹ *Ibid.*

⁵² See <https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml> (March 14, 2018).

⁵³ *Ibid.*

⁵⁴ See <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm> (last visited March 14, 2018).

⁵⁵ *Ibid.*

⁵⁶ See <https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml> (last visited March 13, 2018).

I find that there is an absence of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for migraine that cause suffering.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that cannabis is generally accepted as an effective treatment for anxiety. The Panel discussed medical evidence that cannabis may exacerbate anxiety symptoms or that an effect related to cannabis may be associated with anxiety, such as dependence and cravings. Literature suggests that individuals with anxiety sensitivity may be more likely to turn to cannabis as a mechanism for coping with stress, which may in turn lead to problematic use behaviors.⁵⁷ However, the Panel further discussed a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, which found that there is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, which was assessed by a public speaking test utilizing individuals with social anxiety disorders.⁵⁸ On balance, the Panel recommended adding anxiety as an allowable condition under the MMP as research suggests that it could be helpful to some patients with this condition. I agree. While marijuana may not be effective for all anxiety sufferers, there is research evidencing that it may be helpful to some, especially those with social anxiety disorders. Thus, I find that there is acceptance in the medical community that marijuana is likely to relieve the suffering associated with some anxiety conditions. However, like any medical condition, the use of medical marijuana to treat anxiety must be explored by the medical professional treating the patient to determine whether it is the best and most appropriate course of treatment for the patient.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of anxiety under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of anxiety is “debilitating” and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that anxiety should be added to the MMP.

Opioid Use Disorder

From my independent review of the petitions, I am granting the petition that seeks to add opioid use disorder to the MMP. In coming to this conclusion, I reviewed this condition against the six regulatory criteria cited above and find that it meets the requirements for inclusion in the MMP, with the condition that physicians prescribing medical marijuana for this disorder do so in conjunction with their patient’s medication-assisted treatment, instead of as a singular treatment for the disorder.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that opioid use disorder is a valid condition. According to the U.S. Department of Health and Human Services, Centers for Disease Control

⁵⁷ Anxiety Sensitivity and Distress Intolerance as Predictors of Cannabis Dependence Symptoms, Problems, and Craving: The Mediating Role of Coping Motives. Farris SG, Metrik J, Bonn-Miller MO, Kahler CW, Zvolensky MJ. *J Stud Alcohol Drugs*. 2016 Nov;77(6):889-897.

⁵⁸ The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research, National Academies Press (2017); Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials, *British Journal of Clinical Pharmacology* (2001).

and Prevention, opioid use disorder is “[a] problematic pattern of opioid use that causes significant impairment or distress.”⁵⁹ Additionally, there are multiple ICD-10-CM codes for opioid use disorder.⁶⁰ Because opioid use disorder has a common medical definition and maintains several ICD-10-CM codes, I find that opioid use disorder is a valid condition recognized by the medical community.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. As noted in the petition, the generally accepted treatment for opioid use disorder is medication-assisted treatment (MAT), which includes methadone, naltrexone, and buprenorphine (suboxone). I agree. As stated by the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA), MAT is the “gold standard” for treatment of opioid use disorder.⁶¹ According to SAMHSA, MAT consists of FDA-approved medications, namely methadone, buprenorphine or naltrexone, in combination with behavioral therapies, “to provide a whole-patient approach to the treatment of substance use disorders.”⁶² Side effects from MAT medications include insomnia, headaches, abdominal pain, body aches and vomiting, to name a few.⁶³ Thus, I find that the treatment for opioid use disorder, specifically MAT medications, is recognized and accepted by the medical community. And, while I agree that MAT medications are an effective treatment for opioid use disorder, there are serious side effects that come with this treatment. Accordingly, I also find that MAT medications can cause a patient’s suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient’s ability to carry on activities of daily living, I find that opioid use disorder itself as well as the treatment for this condition cause severe suffering for patients inflicted with this condition. It is without question that opioid use disorder causes severe suffering for an individual stricken with this condition. According to the U.S. Department of Health and Human Services, Office of the Surgeon General, “[o]pioid addiction typically involves a pattern of: (1) intense intoxication, (2) the development of tolerance, (3) escalation in use, and (4) withdrawal signs that include profound negative emotions and physical symptoms, such as bodily discomfort, pain, sweating, and intestinal distress.”⁶⁴ With increased use, the individual not only must take the opioid to avoid the severe withdrawal side effects, but the individual will also experience intense cravings for the opioid and preoccupation with using the opioid.⁶⁵ As such, an individual living with opioid use disorder can experience suffering that ranges from severe psychosocial impairment to overdosing and even death.⁶⁶ With these side effects, a patient is unable to engage

⁵⁹See <https://www.cdc.gov/drugoverdose/opioids/terms.html> (last visited January 17, 2019).

⁶⁰ See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited January 17, 2019).

⁶¹ See https://addiction.surgeongeneral.gov/sites/default/files/Spotlight-on-Opioids_09192018.pdf (last visited January 17, 2019).

⁶² See *Ibid.*

⁶³ See <https://medlineplus.gov/druginformation.html> (last visited January 17, 2019).

⁶⁴ See https://addiction.surgeongeneral.gov/sites/default/files/Spotlight-on-Opioids_09192018.pdf (last visited January 17, 2019).

⁶⁵ *Ibid.*

⁶⁶ *Ibid.*

in activities of daily living, thereby diminishing his or her quality of life. Thus, the condition itself causes the patients with this disorder to suffer immensely.

While opioid use disorder, in and of itself, causes extensive suffering, the treatment for the disorder can also cause significant suffering. Specifically, MAT medications can cause headaches, vomiting, body aches and insomnia.⁶⁷ All of these side effects can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that opioid use disorder as well as the medications used to treat this condition cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatment for opioid use disorder that causes the patient suffering, specifically MAT medications, is the most effective and viable conventional medical therapy offered for this condition. As such, I find that there is an absence of effective alternative medical therapies to the conventional therapies currently prescribed for opioid use disorder that cause patients to suffer.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that there is sufficient evidence that the use of medical marijuana may relieve the suffering related to opioid use disorder when it is used in conjunction with MAT. There is a recent publication by the Cannabis and Cannabinoid Research Journal that sets forth emerging evidence that the use of medical cannabis in conjunction with MAT has the potential to "ease opioid withdrawal symptoms, reduce opioid consumption, ameliorate opioid cravings, prevent opioid relapse, improve [opioid use disorder] treatment retention, and reduce overdose deaths."⁶⁸ However, the publication notes that these findings are preliminary and that additional research, which is hampered by the federal government's designation of marijuana as a Schedule I drug, should be conducted on this promising form of treatment for opioid use disorder.⁶⁹ While I acknowledge that there is little research on the effectiveness of medical marijuana, either alone or in conjunction with MAT, as a treatment for opioid use disorder, given the current opioid epidemic consuming our great State, the citizens of New Jersey suffering from this horrible disorder simply cannot wait for the removal of the political barriers that are preventing research on this promising treatment in order to receive a medication that may ultimately save their lives.

Moreover, as declared under Executive Order No. 219 (2017), "[t]he abuse of and addiction to opioid drugs is a public health crisis in New Jersey, necessitating the marshalling of all appropriate resources to combat its harmful effects on the citizens of our State." This crisis is further evidenced by the staggering number of deaths resulting from opioid overdoses that occur each year in New Jersey. In fact, overdose deaths have more than doubled since 2013. In 2013, there were 1,336 drug-related deaths; in 2016, that number increased to 2,221.⁷⁰ For 2018, the

⁶⁷ See Footnote 6.

⁶⁸ See Wiese B, Wilson-Poe AR (2018) Emerging evidence for cannabis' role in opioid use disorder, Cannabis and Cannabinoid Research 3:1, 179–189, DOI: 10.1089/can.2018.0022.

⁶⁹ *Ibid.*

⁷⁰ See <https://www.njcares.gov/>

number of deaths is projected to jump to a staggering 3,163.⁷¹ With opioid overdose deaths climbing at such an alarming rate, I am compelled to find that the research to date on the beneficial use of medical cannabis as an adjunct to MAT for the treatment of opioid use disorder is sufficient evidence that this form of treatment may alleviate the suffering relating to the disorder and prevent overdose deaths. Indeed, I cannot ignore these disturbing numbers and allow more of our citizens to succumb to this disorder when there is at least some research suggesting that the use of medical marijuana in conjunction with MAT may be an effective treatment for opioid use disorder and ultimately prevent a patient's demise. As such, in giving effect to Executive Order 219's call to garner all possible resources to combat the opioid crisis, I find that the available research I have reviewed establishes sufficient evidence that the use of medical marijuana may relieve the suffering related to opioid use disorder when it is used in conjunction with MAT.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of opioid use disorder under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of opioid use disorder is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition when it is used in conjunction with MAT. As such, I find that opioid use disorder, as a standalone condition, should be added to the MMP.

Denied Petitions

Asthma

After carefully reviewing the petition seeking to include asthma as a debilitating condition under the MMP, and in accordance with the Panel's recommendation, I am denying the request. In coming to this conclusion, I reviewed the petition against the six regulatory factors cited above and found that the condition fails to meet the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that asthma meets this requirement. The CDC defines asthma as a chronic lung disease⁷² that "causes repeated episodes of wheezing, breathlessness, chest tightness, and nighttime or early morning coughing."⁷³ Moreover, the Department recognizes asthma as a chronic medical condition with approximately 600,000 adults and 167,000 children suffering from this condition in New Jersey.⁷⁴ Thus, I find that asthma is generally accepted by the medical community as a valid medical condition.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. In the petition, the petitioner asserts that the use of albuterol to treat asthma causes an individual to experience an increased heart rate and shakiness and that the use of corticosteroids to treat asthma can cause the patient to become

⁷¹ *Ibid.*

⁷² See https://www.cdc.gov/asthma/stateprofiles/asthma_in_nj.pdf (last visited March 13, 2018).

⁷³ See <https://www.cdc.gov/asthma/default.htm> (last visited March 13, 2018).

⁷⁴ See <http://www.nj.gov/health/fhs/chronic/asthma/in-nj/> (last visited March 13, 2018).

addicted to the drug. While corticosteroids and bronchodilators, such as albuterol, are generally accepted treatments for asthma, I do not find that the average patient suffers from the use of these medications. As stated by the Panel, there are several treatments for asthma that are not only effective but also provide minimal side effects. Specifically, asthma is generally treated with inhaled, oral and intravenous corticosteroids and bronchodilators.⁷⁵ Common side effects associated with the use of corticosteroids include acne, weight gain and upset stomach.⁷⁶ However, these side effects rarely occur with the short-term use of these medications, such as when they are used for acute asthma episodes.⁷⁷ While the use of corticosteroids is accepted by the medical community as valid treatments for asthma, I do not find that these treatments cause the vast majority of patients to experience suffering from their use.

The same holds true for bronchodilators. While bronchodilators can cause nervousness or shakiness, headache, throat or nasal irritation, muscle aches and, in rare instances, a rapid heart rate or heart palpitations, these side effects can be greatly reduced and even eliminated by changing the delivery method of the medication and/or reducing the dosage.⁷⁸ Although these side effects could potentially cause a patient to suffer, they can be effectively decreased and even eliminated through medication management. As such, I find that the treatments for asthma do not cause an average asthma patient to experience suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that asthma can cause severe suffering. Specifically, when asthma is not well-controlled, it can severely impair a patient's ability to engage in his or her activities of daily living, such as limiting the patient's physical activity, cause sleep disturbances and can even result in death. Accordingly, I find that asthma can cause a patient to experience severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. While asthma cannot be cured, it can be well-controlled with self-management education, adequate pharmacological management, and avoidance of exposure to environmental triggers.⁷⁹ Specifically, asthma is commonly and effectively treated with bronchodilators and corticosteroids, which are widely available to patients and have little side effects.⁸⁰ Thus, I find that the conventional medical treatments for asthma are effective and easily attainable by patients.

Regarding the fifth factor, which whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there are no reliable clinical trials or research supporting the proposition that medical cannabis is an effective treatment for asthma. While the petitioner points

⁷⁵ See <https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660> (last visited March 13, 2018).

⁷⁶ See <https://my.clevelandclinic.org/health/diseases/16864-treating-the-inflammation-of-asthma> (last visited March 13, 2018).

⁷⁷ *Ibid.*

⁷⁸ See <https://www.mayoclinic.org/diseases-conditions/asthma-attack/expert-answers/albuterol-side-effects/faq-20058088> (last visited March 13, 2018).

⁷⁹ See <https://www26.state.nj.us/doh-shad/topic/Asthma.html> (last visited March 13, 2018).

⁸⁰ See Footnote 62.

to a study published in the New England Journal of Medicine in 1973, which suggests that marijuana dilates the airway for a short period of time, the study did not evaluate the effect marijuana has on patients suffering from asthma. In fact, the study utilized thirty-two male subjects with no serious medical conditions and advised that “further investigation is required to determine . . . the effects of marijuana smoking and oral THC on the airway of asthmatic subjects.” As such, I find that this study does not support the proposition that marijuana is an effective treatment for asthma.

Even more, physicians with the American Thoracic Society recently published an article in the American Journal of Respiratory and Critical Care Medicine advising that marijuana can worsen existing lung conditions and specifically noted that “marijuana smoke can cause an asthma attack leading to hospitalization and even death.”⁸¹ Thus, the medical community appears to be opposed to the use of marijuana as a treatment for asthma. Because the petitioner failed to point to any evidence demonstrating that the medical community accepts medical marijuana as a treatment for asthma, and neither I nor the Panel found any reliable trials or research in support of this, I find that the medical community is not in favor of using medicinal cannabis to alleviate the suffering associated with asthma.

As for the final factor, which is whether there are letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of asthma under the MMP, I find that the petition only referenced the 1973 New England Journal of Medicine article and did not include any letters of support from healthcare professionals. While the journal article was authored by three physicians, I do not find that this lone article from 1973 on the general effects of marijuana on the airway constitutes support from a medical professional for the inclusion of asthma to the MMP. Additionally, there were no public comments from medical professionals supporting the inclusion of asthma under the MMP. Thus, I find that there is a lack of support from physicians or other health care professionals for this condition to be added to the MMP.

Based upon the foregoing, I find that asthma can be debilitating if uncontrolled, but that marijuana is not likely to be a beneficial treatment for this condition or alleviate the debilitating effect of this condition. Indeed, as noted by the Panel, inhalation of smoke is a known trigger for asthma exacerbation and, as a result, smoking marijuana may actually increase the suffering of asthma patients rather than alleviate the suffering associated with this condition⁸². And, while I acknowledge that medicinal marijuana is available in non-smokable forms, I am not convinced that there is credible support for its use in treating asthma. Unless and until there is sufficient research and evidence demonstrating that the use of marijuana can be beneficial for an asthma patient, I find that asthma should not be added to the MMP.

Chronic Fatigue Syndrome

From my detailed review of the petition seeking to include chronic fatigue syndrome as a debilitating condition under the MMP, and in accordance with the Panel’s recommendation, I have concluded that the petition should be denied. In coming to this conclusion, I reviewed the petition

⁸¹ Drake MD, Matthew G. and Slatore MD, Christopher G. “Smoking Marijuana and the Lungs.” Am. J. Respir. Crit. Care Med., Vol. 195, P5-6 (2017).

⁸² Ibid.

against the six regulatory factors cited above and found that the condition fails to meet the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic fatigue syndrome meets this criteria. According to the CDC, chronic fatigue syndrome, also known as myalgic encephalomyelitis, is a “long-term illness that affects many body systems.”⁸³ In addition to extreme fatigue, which may worsen with physical or mental activity, but does not improve with rest, an individual with this condition may experience insomnia, depression, joint and muscle pain and memory impairments.⁸⁴ In fact, there is an estimated 836,000 to 2.5 million individuals affected with this condition in the United States.⁸⁵ Thus, I find that chronic fatigue syndrome is a valid medical condition.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. Unfortunately, there is neither a cure nor an FDA-approved treatment for chronic fatigue syndrome.⁸⁶ As a result, treatment is largely palliative as the treatment is tailored to relieve the symptoms experienced by each individual patient. For example, a patient experiencing depression as a result of chronic fatigue syndrome could be treated with an anti-depressant and a patient experiencing muscle and joint pain could be prescribed an NSAID to relieve the pain.⁸⁷ Moreover, the symptoms of chronic fatigue are oftentimes treated with nutritional supplements and complementary therapies, such as massage, meditation, tai chi and acupuncture, which may be helpful in increasing the patient’s energy level and decreasing his or her pain.⁸⁸ But, these are not treatments for the actual condition but rather treatments for the symptoms associated with the condition. As such, I find that there is no treatment generally accepted in the medical community for this disease that causes suffering.

However, I do find that the above therapies prescribed by healthcare professionals to treat the **symptoms** associated with chronic fatigue syndrome are accepted by the medical community. While I find that the treatments for chronic fatigue symptoms are medically acceptable, the specific treatment prescribed depends on the type and severity of the symptoms presented and can range from anti-depressants and NSAIDs, which can have severe side effects for some patients and thereby cause suffering, to massage therapy and acupuncture, which have little to no side effects. Because there is a vast array of treatment options for chronic fatigue symptoms and no two patients are treated the same, I am unable to conclude that chronic fatigue patients generally suffer from the treatments they receive for their symptoms. However, individuals with severe forms of chronic fatigue syndrome may suffer from the treatments used to alleviate their symptoms.

⁸³ <https://www.cdc.gov/me-cfs/index.html> (last visited March 13, 2018).

⁸⁴ <https://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/symptoms-causes/syc-20360490> (last visited March 13, 2018).

⁸⁵ Wright Clayton, MD, Ellen, “Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome An IOM Report on Redefining an Illness.” JAMA (2015).

⁸⁶ <https://www.cdc.gov/me-cfs/treatment/index.html> (last visited March 13, 2018).

⁸⁷ <https://www.cdc.gov/me-cfs/index.html> (last visited March 13, 2018).

⁸⁸ *Ibid.*

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that chronic fatigue syndrome can cause severe suffering. Specifically, some individuals suffering from chronic fatigue syndrome can experience severe pain, gross memory loss and even such extreme fatigue that the patient is house-bound or even bed-bound, all of which greatly impacts a patient's ability to engage in activities of daily living and maintain a quality life. Accordingly, I find that chronic fatigue syndrome can cause a patient to experience severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. While chronic fatigue cannot be cured and there is no approved treatment for the condition, there is a wide array of pharmacological therapies available for alleviating the symptoms associated with this condition. Specifically, chronic fatigue symptoms can be effectively managed for some patients with NSAIDs, anti-depressants and sleep-aids, depending on the severity and type of symptoms presented. However, depending upon the patient, the pharmacological treatments for chronic pain symptoms may be effective but may also cause the patient to suffer from side effects. Thus, I find that there are available conventional medical therapies to alleviate a chronic fatigue patient's suffering, but those treatments may cause suffering for some patients.

Regarding the fifth factor, whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there are no reliable clinical trials or research supporting the proposition that medical cannabis is an effective treatment for chronic fatigue syndrome. While the petitioner points to studies suggesting that medical marijuana can alleviate an individual's pain, which is potentially one symptom a patient inflicted with chronic fatigue syndrome may experience, the studies fail to articulate that marijuana is an effective treatment for the condition of chronic fatigue syndrome as a whole. Because the petitioner failed to point to any evidence demonstrating that the medical community accepts medical marijuana as a treatment for the actual condition of chronic fatigue syndrome, and neither I nor the Panel found any credible clinical evidence in support of this, I find that there is a lack of support in the medical community for the use of medicinal cannabis to alleviate the suffering associated with chronic fatigue syndrome.

As for the final factor, which is whether there are letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic fatigue under the MMP, I find that the petition only referenced the above-mentioned studies reflecting on the effectiveness of medical marijuana to treatment pain and did not include any letters of support from healthcare professionals to have chronic fatigue added to the MMP. Additionally, there was an absence of public comments from medical professionals supporting the inclusion of chronic fatigue under the MMP. Thus, I find that there is a lack of support from physicians or other health care professionals for this condition to be added to the MMP.

Based upon the above analysis, I find that chronic fatigue syndrome can be debilitating for some patients, but that medical marijuana is not likely to be a potentially beneficial treatment for the debilitating effect of this condition or the alleviation of the symptoms associated with this condition. Indeed, as noted by the Panel, this condition has been researched for years and there is yet to be found a solid elucidation of the etiology of this condition or the treatments that are

effective for it.⁸⁹ Because there are still so many unknowns with this condition and there is no clinical evidence suggesting that marijuana would be beneficial as a treatment, I find that chronic fatigue syndrome should not be added to the MMP at this time.

Conclusion

Based upon the foregoing, I am adding chronic pain associated with musculoskeletal disorders, chronic pain of a visceral origin, as well as Tourette's Syndrome, migraine, anxiety and opioid use disorder (with the condition that medical marijuana be prescribed in conjunction with medication-assisted therapy for the treatment of the disorder) to the MMP. However, asthma and chronic fatigue syndrome will not be added to the MMP.

In order to provide patients with relief as soon as possible from the suffering they are experiencing from these debilitating conditions, I am immediately adding chronic pain associated with musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, anxiety and opioid use disorder to the MMP in advance of rule promulgation. While I am including these conditions under the MMP, please note that this decision is not intended to be a blanket endorsement for every patient inflicted with a condition falling under the MMP to utilize medicinal marijuana as a treatment. As with any condition, the course of treatment must be determined by a medical professional after a thorough evaluation and discussion with the patient regarding the benefits and possible negative effects of the recommended therapy. Accordingly, I encourage patients to discuss the possibility of utilizing medical marijuana as a treatment for their debilitating conditions with the medical professionals treating them. I hope that this decision brings needed relief to those suffering with these conditions.

This is a final agency decision. You have the right to appeal this final agency decision within 45 days to the New Jersey Superior Court, Appellate Division, Richard J. Hughes Justice Complex, P.O. Box 006, Trenton, New Jersey 08625-0006.



Shereef M. Elnahal, MD, MBA
Commissioner

⁸⁹ <https://www.ncbi.nlm.nih.gov/books/NBK293931/> (last visited March 13, 2018).

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

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