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

**Instructions** Medical Cannabis Registry

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 **Wednesday, February 20, 2019.** 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 Waialae Avenue, #648, Honolulu, Hawaii 96816.Mailed petitions must be received by **Wednesday, February 20, 2019.**

   c. Hand delivered to: Kinau Hale at 1250 Punchbowl Street, Honolulu, Hawaii 96813 before the close of business (4:30PM) on **Wednesday, February 20, 2019**.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

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

**Petitioner Content**

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

Opioid Use Disorder DSM-5 F11.10 F11.20

**(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.**

We are in the depths of an opiate epidemic  opiate overdoses are the leading cause of accidental death in both the United States and Canada . There have been numerous studies showing the effectiveness of Cannabis for treating pain. The most influential one was the 2017 study done by the National Academy of Sciences, Engineering and Medicine. This study did a comprehensive literature review and found that Cannabis is a safe and effective way to treat pain, both acute and chronic (1). Cannabis can be used in conjunction with Opiates and can decrease opiate use. In 2018 JAMA published a study showing that in states where medical cannabis was available Opiate prescriptions decreased by 5.88% in Medicaid enrollees. In states where adult-use cannabis is available, opiate prescriptions in Medicaid enrollees decreased by 6.38%. (2) Furthermore, there was a decrease in Opiate overdoses in States with Medical Cannabis laws (MCL). States with cannabis laws saw a decrease in opiate deaths by 24% from 1990-2010. (2,3,4). Cannabis and opiates work synergistically and can increase pain control when used together. Cannabis is opiate sparring and doesn't decrease respirations. (5). Cannabis can also be combined with opiates to treat patients with advanced cancer and hard to treat pain (6). MAT or Medication Assisted Treatment (for opiate use) "Results suggest that cannabis use strengthens, rather than weakens, the relationships between pain and depression and pain and anxiety. These effects appear to be driven by decreased self-efficacy in cannabis users. It is important to understand how self-efficacy can be improved through symptom self-management interventions and whether self-efficacy can improve distressing symptoms for people in MAT." (7). Another study in 2016 showed that women who used cannabis while on a MAT program had better treatment outcomes (8).

**(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.**

DSM 5 Diagnostic criteria

Opioids are often taken in larger amounts or over a longer period of time than intended. There is a persistent desire or unsuccessful efforts to cut down or control opioid use. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects, craving, or a strong desire to use opioids. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids. Important social, occupational or recreational activities are given up or reduced because of opioid use. Recurrent opioid use in situations in which it is physically hazardous Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids. *Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid *Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid. (9)

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

**(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.**

Opioid Use Disorder DSM-5 F11.10 F11.20 has many symptoms. Clinicians have been using well-established tools as a guideline to manage symptoms of opioid use disorder. CINA and COWS are used widely in inpatient and outpatient settings. They list the most common symptoms of opioid use disorder.
Anxiety
Temperature changes
GI upset
Abdominal pain
Restlessness
Bone or joint aches
Sweating
Runny nose/Tearing
Tremor
Gooseflesh
Yawning
Pupil size
Pulse rate
Systolic Blood pressure (10)

**(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.**

MAT, medication-assisted therapy, is the standard for Opioid Use Disorder DSM-5 F11.10 F11.20. In the above literature review, I highlight articles that show MAT, when combined with cannabinoid therapy is a viable option

**(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.**

MAT or Medication-Assisted Therapy

Suboxone has similar outcomes to methadone and in some studies at one year follow up 75% of patients are still in treatment (Valander 2018). Suboxone and methadone programs are limited in Hawaii and in the US. The DOH lists substance abuse treatment centers in our state 14 on Oahu 2 on Hawaii island, 3 on Maui 1 on Molokai and 2 on Kauai. (DOH, 2019) With a population of almost 1.42 million, the shortage of

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

treatment options is apparent.

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

**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.**

**Cannabis annd Opiate Use Disorder:** Cannabis can be used in conjunction with Opiates and can decrease opiate use. In 2018 JAMA published a study showing that in states where medical cannabis was available Opiate prescriptions decreased by 5.88% in Medicaid enrollees. In states where adult-use cannabis is available, opiate prescriptions in Medicaid enrollees decreased by 6.38%. (2) Furthermore, there was a decrease in Opiate overdoses in States with Medical Cannabis laws (MCL). States with cannabis laws saw a decrease in opiate deaths by 24% from 1990-2010. (2,3,4).

Cannabis and opiates work synergistically and can increase pain control when used together. Cannabis is opiate sparring and doesn't decrease respirations. (5). Cannabis can also be combined with opiates to treat patients with advanced cancer and hard to treat pain (6).

MAT or Medication Assisted Treatment (for opiate use) "Results suggest that cannabis use strengthens, rather than weakens, the relationships between pain and depression and pain and anxiety. These effects appear to be driven by decreased self-efficacy in cannabis users. It is important to understand how self-efficacy can be improved through symptom self-management interventions and whether self-efficacy can improve distressing symptoms for people in MAT." (7). Another study in 2016 showed that women who used cannabis while on a MAT program had better treatment outcomes (8).

**Anxiety:** Cannabis in preclinical and clinical trials has shown some efficacy as an anxiolytic. Cannabis CBD is showing potential in fear extinction, assisting in compulsion, and aiding in stress-induced anxiety (11). In a 2019 study, Dr. Hurd showed that CBD can reduce the craving for heroin and decrease anxiety in drug abstinent heroin users over placebo. (12)

**Nausea:** Cannabis has been used for thousands of years for nausea and it continues to be used for nausea in several settings. Patients receiving chemotherapy often experience debilitating nausea. Cannabis has similar outcomes when compared to other medications in controlling nausea for patients receiving chemotherapy (14).Cannabis blocks both acute and delayed nausea, and can be more effective than many modern drugs (15)

**(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.**

Use of Cannabis in adolescent rats show an increase in Herion use in adult rats, In a study 90%of Herion users report a history of cannabis use, opposed to 47% who report using prescription (15)

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

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


# Thomas Cook, M.D.

*Psychiatry & General Mental Health*
*1401 S. Beretania St. Suite 340*
*Honolulu, HI, 96814*


Date: 7-20-19

To Whom It May Concern:

I am writing this letter in support of a provision to include patients with opioid dependency in Hawaii's medical cannabis program.

In my clinic we have extensive experience treating opioid dependence with psychotherapy, counseling, and medication management. I frequently prescribe suboxone, (*buprenorphine*) an opioid replacement drug, for the treatment of opioid dependence. I also certify for medical cannabis for PTSD and severe pain and other conditions, thus, I sometimes see patients who are attempting to stop using opioids and who also have a cannabis card. Thus, my practice is ideal as an intersection of these two issues, opioids and cannabis. I do not prescribe traditional opioid medications, since I am a psychiatrist, however, I am intimately familiar with both opioids in their effects, since many patients come to me already addicted to them.

My evidence is anecdotal, however, I can say that within my practice, a person's chance of stopping opioids nearly doubles if they are also utilizing medical cannabis. The statistics show that suboxone helps people get off opioids about 30% of the time, and that is generally what I have seen for my patients who do not have a medical cannabis card. However, among my opioid addicted patients that do have a cannabis card, I would estimate their chance of stopping opioids rises to about 50%.

My numbers are anecdotal, however, they are based on many dozens of patients I have seen over the years. In the realm of addiction treatment, 50% is remarkable. The groups, Narcotics and Alcoholics Anonymous, are by comparison no more than 5-10% effective.

This anecdotal data concurs with old wisdom: prior to the prohibition of cannabis in the late 1930's, cannabis was understood to have an opiate-sparing effect.

There was an old mixture of morphine, cannabis, and capsicum (pepper) that was extremely popular back then, called *Chloranodyne*. This was in most doctor's bags in the early 1900's. It was manufactured by the Parke-Davis drug company in Michigan. It was common sense back then that cannabis oil reduced the nausea and constipation and poor appetite commonly caused by morphine. It was mixed into pain preparations because it helped doctors give less morphine.

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

We have reached such a crisis today that some hospitals in the third world have shortages of morphine due to excessive use of morphine. Americans consume 80% of the world's opioids, but are 5% of the world's population. I have heard stories, as a physician, of family members dying from prescription opiate medication mixing with other deadly medications. It breaks my heart to hear these stories over and over, when cannabis is now available for pain and has never been known to be fatal to anyone.

Many of the opioid addicted patients get started by using opioids as chronic pain medications, (or after a surgery), and then they transition into full blown addiction. Thus, chronic pain- a certifiable condition- is an issue with a large degree of overlap with opioid addiction, unfortunately. Thus, if medical cannabis helps reduce opioid use among patients with severe chronic pain, it is highly likely to reduce opioid usage among patients who do not have a pain issue, but are simply addicted to opioids. It is well known that opioids sensitizes the brain to various normal aches and pains, and many opioid addicted patients begin to complain of pain. Again, the demographic overlap is significant.

Please allow me to quote from one study published in *JAMA Internal Medicine* on April 2, 2018.

The authors were Wen, and Hockenberry: they looked at opioid prescriptions from 2011 to 2016. Eight states utilized medical cannabis during that timeframe: Connecticut, Delaware, Illinois, Maryland, Massachusetts, Minnesota, New Hampshire, and New York. Four other states had recreational adult use: Alaska, Colorado, Oregon, and Washington. The states with medical cannabis laws were found to have a 6% decrease in opioid prescriptions. Whereas recreational states had a 9.78% decrease in opioid prescriptions.

These numbers are incredibly important, because they look at number of prescriptions, not the dose of the opioid. These studies do ***not*** discuss reduction in opioid dosage, only discontinuation of use (or reduction in prescription counts, which is roughly the same thing.)

Thus, it is likely that the reduction in opioid dosage in recreational states is much higher than 9.78%. On a large scale, this is a life-saving difference.

*JAMA* has published other articles worth reviewing, such as the one by Ashley Bradford on the reduction in medicare part D prescriptions for opioids.

The evidence is both old and new that medical cannabis is very helpful to both prevent, and treat, opioid dependence, and I would urge the Hawaii legislature to consider adding opiate dependence to the list of certifiable conditions.

I am a licensed physician, in state of HI, MD license 16978, expiration date 1/31/2020.

You may call my business line with any questions.

Cordially,

Thomas Cook, M.D.
*Ph# (808) 457-1082 Fx# (808) 356-1649* [*www.drcook.org*](http://www.drcook.org)

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

You **MUST** provide a Number and Name for each Attachment referenced above and provide a list of these attachments here. This way we can ensure that your petition was submitted with all of the applicable attachments:

References

1.National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press.

doi: 10.17226/24625.

Cannabis decreasing Opiate use

2. Wen H, Hockenberry JM. Association of Medical and Adult-Use Marijuana Laws with Opioid Prescribing for Medicaid Enrollees. JAMA Intern Med. 2018;178(5):673–679. doi:10.1001/jamainternmed.2018.1007

Cannabis decreasing opiate overdose deaths

3. Philippe, Lucas. Rationale for cannabis-based interventions in the opioid overdose crisis. Harm Reduction Journal. 2018

doi: 10.1186/s12954-017-0183-9

4. Melvin D. Livingston, Tracey E. Barnett, Chris Delcher, Alexander C.Wagenaar, "Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000–2015", American Journal of Public Health 107, no. 11 (November 1, 2017): pp. 1827-1829.

doi: 10.2105/AJPH.2017.304059

Cannabis and opiates increase pain control when used together

5. Ziva D. Cooper et al. Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability Neuropsychopharmacologyvolume 43, pages2046–2055 (2018)

DOI: 10.1038/s41386-018-0011-2

6. Fallon, M. T., Lux, E. A., McQuade, R., Rossetti, S., Sanchez, R., Sun, W., … Kornyeyeva, E. (2017). Sativex Oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. British Journal of Pain, 11(3), 119–133.

doi:https://doi.org/10.1177/2049463717710042

Cannabis used to assist in decreasing opiate use

7. Marian, Wilson et all Cannabis use Moderates the Relationship Between Pain and Negative Affects in Adults with opioid use disorder. Addictive Behaviors, Volume 77 (2), 225-221

doi: https://doi.org/10.1016/j.addbeh.2017.10.012

8. Zylinkski, Lauren et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. Biology of Sex Differences20178:8

https://doi.org/10.1186/s13293-017-0130-1

9. DSM IV OUD https://www.ncbi.nlm.nih.gov/books/NBK535277/box/p2.b4/?report=objectonly

10. D. Andrew Tompkins, M.D.1, George E. Bigelow, Ph.D.1, Joseph A. Harrison, B.S.1, Rolley E. Johnson, Pharm.D.1,2, Paul J. Fudala, Ph.D.2, and Eric C. Strain, M.D.1
Drug Alcohol Depend. 2009 November 1; 105(1-2): 154–159.
doi:10.1016/j.drugalcdep.2009.07.001.

11. Esther M. Blessing, Steenkamp, J. Manzanares, C. Marmar Cannabidiol as a Potential Treatment for Anxiety Disorders; Neurotherapeutics (2015) 12:825–836
DOI 10.1007/s13311-015-0387-1

12. Hurd, et al, Cannabidiol for the reduction od Cue Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double Blind Randomized Placebos- Controlled Trial; American Journal of Psychiatry (2019)
https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2019.18101191

13. Beth Wiese and Adrianne R. Wilson-Poe, Emerging Evidence for Cannabis' Role in Opioid Use Disorder Cannabis and Cannabinoid Research Volume 3.1, 2018
DOI: 10.1089/can.2018.0022

14. Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD009464.

15. Sharkey, K.A., Damani, M.A., Parker,L.A. Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system EUR J Pharmacol, (2014) 722; 134- 136

doi: 10.1016/j.ejphar.2013.09.068

16. Finn Kenneth. Why Marijuana Will Not Fix the Opioid Epidemic. Mo Med (2018) 115; 3 191-193
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140166/pdf/ms115_p0191.pdf

# REFERENCE #1

(PDF was not submitted)

# REFERENCE #2

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

# Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees

Hefei Wen, PhD; Jason M. Hockenberry, PhD

**IMPORTANCE** Overprescribing of opioids is considered a major driving force behind the opioid epidemic in the United States. Marijuana is one of the potential nonopioid alternatives that can relieve pain at a relatively lower risk of addiction and virtually no risk of overdose. Marijuana liberalization, including medical and adult-use marijuana laws, has made marijuana available to more Americans.

**OBJECTIVE** To examine the association of state implementation of medical and adult-use marijuana laws with opioid prescribing rates and spending among Medicaid enrollees.

**DESIGN, SETTING, AND PARTICIPANTS** This cross-sectional study used a quasi-experimental difference-in-differences design comparing opioid prescribing trends between states that started to implement medical and adult-use marijuana laws between 2011 and 2016 and the remaining states. This population-based study across the United States included all Medicaid fee-for-service and managed care enrollees, a high-risk population for chronic pain, opioid use disorder, and opioid overdose.

**EXPOSURES** State implementation of medical and adult-use marijuana laws from 2011 to 2016.

**MAIN OUTCOMES AND MEASURES** Opioid prescribing rate, measured as the number of opioid prescriptions covered by Medicaid on a quarterly, per-1000-Medicaid-enrollee basis.

**RESULTS** State implementation of medical marijuana laws was associated with a 5.88% lower rate of opioid prescribing (95% CI, −11.55% to approximately −0.21%). Moreover, the implementation of adult-use marijuana laws, which all occurred in states with existing medical marijuana laws, was associated with a 6.38% lower rate of opioid prescribing (95% CI, −12.20% to approximately −0.56%).

**CONCLUSIONS AND RELEVANCE** The potential of marijuana liberalization to reduce the use and consequences of prescription opioids among Medicaid enrollees deserves consideration during the policy discussions about marijuana reform and the opioid epidemic.

*JAMA Intern Med*. 2018;178(5):673-679. doi:10.1001/jamainternmed.2018.1007
Published online April 2, 2018.

Invited Commentary page 679
Author Audio Interview
Related article page 667
Supplemental content
CME Quiz at jamanetwork.com/learning

**Author Affiliations:** Department of Health Management & Policy, University of Kentucky College of Public Health, Lexington (Wen); Department of Health Policy & Management, Emory University Rollins School of Public Health, Atlanta, Georgia (Hockenberry); National Bureau of Economic Research (NBER), Cambridge, Massachusetts (Hockenberry).

**Corresponding Author:** Hefei Wen, PhD, Department of Health Management & Policy, University of Kentucky College of Public Health, Lexington, KY 40536 (hefei.wen@uky.edu).

Overprescribing of opioids for pain management is considered a major driving force behind the opioid epidemic in the United States[1,2] A concerted policy effort has been made during the past decade to regulate opioid-prescribing practices.[3] As access to prescription opioids becomes increasingly restricted, there is growing concern that restrictions on prescription opioids may have pushed those already addicted to opioids to seek more dangerous drugs and sources.[4]

The potential unintended consequences of restricting access to prescription opioids has shifted some policy attention to the development and use of nonopioid alternatives.[5,6] Marijuana is one of the potential alternative drugs that can provide relief from pain at a relatively lower risk of addiction and virtually no risk of overdose.[7-9] The therapeutic value of marijuana has been one of the central rationales behind the marijuana liberalization policies in many states that now allow marijuana use for medical and adult-use purposes.[10] On the one hand, proponents of these medical and adult-use marijuana laws tout marijuana liberalization as a potential solution to the excessive use of opioids.[5,6,10] Some opponents, on the other hand, view marijuana as a "gateway" or "stepping stone" to opioids and worry that marijuana liberalization may exacerbate the opioid epidemic.[6,11]

Although both medical and adult-use marijuana laws, in principle, have made marijuana available to more Americans, the laws targeted different groups and may have different opioid-related consequences. In medical marijuana laws, states typically specify a list of conditions that are eligible for medical marijuana, and most states have included in the list generic terms such as "severe pain," "chronic pain," or "intractable pain unrelieved by standard medical treatment and medications." Patients with eligible conditions are expected to obtain recommendation from qualified physicians and enroll in a patient registry. Patients are then issued identification cards that allow them or their caregivers to possess a certain amount of marijuana through home cultivation and licensed dispensaries (in some states these are called "compassionate centers").[10] As a result, medical marijuana laws may have affected pain management for only a selected group of patients with pain and with state-specified eligible conditions, sources of care from licensed marijuana physicians, and ready access to marijuana.

Adult-use marijuana laws, which to date have been enacted only in states with existing medical marijuana systems, fundamentally restructured the distribution and possession of marijuana. Unlike the eligibility criteria and registry and/or renewal process under medical marijuana laws, adult-use marijuana laws permit all adults 21 years or older to use marijuana. Furthermore, marijuana supply channels have often been expanded through grow operations and retail dispensaries licensed and taxed by the states.[10] Thus, adult-use marijuana laws enable individuals without eligibility or access to medical marijuana before such laws to use marijuana as self-medication for pain conditions. A potential repercussion of adult-use marijuana laws, however, is that the outright legalization/taxation message conveyed by the laws may encourage individuals to normalize the risky behaviors in general.[12]

Empirical studies on medical marijuana laws have indicated downstream policy effects on reducing opioid-related hospitalizations, opioid overdose deaths, and opioid-involved traffic fatalities.[5,13,14] Furthermore, Bradford and Bradford[15,16] found evidence that the implementation of medical marijuana laws reduced the number of prescriptions used to treat the conditions, including pain, which most states have deemed eligible for medical marijuana. However, the authors did not single out prescription opioids. The prescription opioids were aggregated with nonopioid analgesics and 9 other classes of drugs broadly classified as pain-related prescriptions (eg, antidepressants, muscle relaxants, respiratory inhalant products, functional bowel disorder agents).

Regarding adult-use marijuana laws, only 1 study to date has examined the policy effect on opioid-related health outcomes. Livingston and colleagues[17] found an interrupted reversal of the upward trend in Colorado's opioid overdose mortality when the state legalized adult-use marijuana use. No study to date has focused on the effect of medical and adult-use marijuana laws on opioid prescribing in particular.

We examined the opioid prescribing rates among Medicaid enrollees in the context of state marijuana liberalization policies between 2011 and 2016. During this period, an estimated one-third of opioid prescriptions were misused or abused, of which Medicaid shared a disproportionately large burden.[18] In addition to opioid prescribing rates, we also studied Medicaid spending on prescription opioids, as well as the prescribing rates of, and spending on, nonopioid pain medications. As medical and adult-use marijuana laws continue to gather momentum in state legislatures, the study findings are informative for states' implementation and iterations of marijuana reform as well as the nation's fight against the opioid epidemic.

### Key Points

**Question** Are medical and adult-use marijuana laws passed after 2010 associated with lower rates of opioid prescribing for Medicaid enrollees?

**Findings** In this population-based, cross-sectional study using the all-capture Medicaid prescription data for 2011 to 2016, medical marijuana laws and adult-use marijuana laws were associated with lower opioid prescribing rates (5.88% and 6.38% lower, respectively).

**Meaning** Medical and adult-use marijuana laws have the potential to lower opioid prescribing for Medicaid enrollees, a high-risk population for chronic pain, opioid use disorder, and opioid overdose, and marijuana liberalization may serve as a component of a comprehensive package to tackle the opioid epidemic.

## Methods

### Data

This study was exempt from institutional review board review. The primary data source for this study was the State Drug Utilization Data from the Centers for Medicare and Medicaid Services (CMS).[19] All states are required to report to CMS quarterly on the amount of all outpatient drug prescriptions covered by Medicaid fee-for-service and managed care in exchange for federal matching funds. We excluded a few observations from the study data owing to the inconsistency in state data reporting. The study sample includes 1059 state-quarter observations.

We used data from the first quarter of 2011 to the second quarter of 2016; 2011 is the first year in which state reporting of Medicaid managed care prescription data became mandatory and nearly complete under the Affordable Care Act (ACA) data collection requirements. The managed care data captures many high-risk low-income adult enrollees who recently gained Medicaid coverage under the expansion provisions of the ACA or the Section 1115 waiver. These low-income adults included in the recent expansion are shown to have disproportionately high risks for chronic pain, as well as opioid use disorder and overdose.[20] Another reason behind our choice of the study window is that it minimizes the influence of some nationwide policies and guidelines that were in place before 2011 or were about to be announced in 2016. These major common changes include, but are not limited to, the 2010 OxyContin reformulation, the publication of 2 national guidelines for appropriate opioid prescribing in chronic pain management in 2009 and 2010, the Surgeon General's warning letter about opioid crisis in 2016, and the Centers for Disease

Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain and the subsequent state laws aligned with the CDC guideline that limit the opioid prescribing duration.[21-25]

## Measures

Our primary outcome of interest was the state-level opioid prescribing rate, defined as the number of opioid prescriptions that were primarily used for pain management and covered by Medicaid on a quarterly, per-1000-Medicaid-enrollee basis in each state. Each opioid product in the data was identified by a unique 11-digit, 3-segment National Drug Code (NDC) number. We classified opioid products into 2 categories based on the Controlled Substance Act scheduling: Schedule II opioids and Schedule III to V opioids. The Schedule II opioids are generally considered to have a higher addiction rate and overdose liability. Since October 2014, hydrocodone combination products have been rescheduled from Schedule III to Schedule II.[26] Accordingly, we classified all hydrocodone combination products as Schedule II opioids throughout the entire study period. We excluded the opioid products that were primarily used for medication-assisted treatment of opioid use disorder and for conditions other than pain (eg, codeine-containing cough and cold medications). In addition to the main outcome of opioid prescribing rates, we also studied Medicaid spending on prescription opioids, as well as the prescribing rates of, and spending on, nonopioid pain medications. (See the Supplement for the detailed information on variable measurement.)

The key independent variables are an indicator for the implementation of medical marijuana laws and an indicator for the implementation of adult-use marijuana laws. The policy indicators were assigned a value of 1 for each full quarter subsequent to the effective date of the medical or adult-use marijuana law in a state, and a value of 0 for the premedical marijuana or pre–adult-use marijuana law quarters and for the comparison states. The medical marijuana law indicator captures the association between medical marijuana law implementation and opioid prescribing relative to no marijuana law. The adult-use marijuana law indicator captures the association between adult-use marijuana law implementation and opioid prescribing in the context of an existing medical marijuana law because no states without a medical marijuana law have adopted an adult-use marijuana law.

The 2 main policy indicators treat medical marijuana laws and adult-use marijuana laws as 2 homogeneous sets of laws between states and across time. Furthermore, we explored the heterogeneous policy effects using 12 separate indicators for 8 state medical marijuana laws and 4 state adult-use marijuana laws. The state-specific policy effects help provide further insights into the potential policy heterogeneity associated with differences in statutory language, enforcement experience, and policy environments across states.[27] (See the Supplement for a summary of medical marijuana laws and adult-use marijuana laws.)

## Statistical Analyses

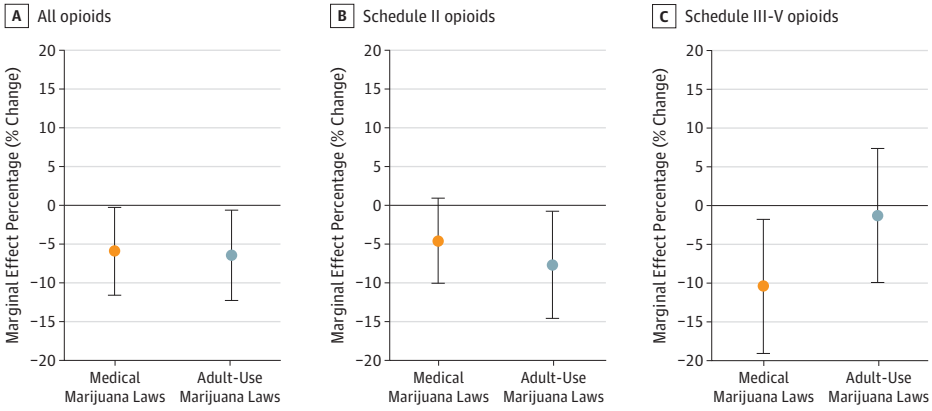
We used a quasi-experimental difference-in-differences design, which is analogous to an adjusted pre-post trend difference analysis. In modeling this, we used a state and quarter fixed-effects approach that has commonly been used in multistate, multipolicy evaluations. This 2-way fixed-effects approach allows us to account for unobserved differences across states that were constant over time, as well as nation-wide secular trends that were correlated with prescription opioid use (eg, nationwide leveling off and gradual reduction in annual opioid prescribing rate, rising public awareness of the role of opioids in pain management and the role of buprenorphine in opioid use disorder treatment).[28]

All models were population-weighted and adjusted for state-level characteristics that varied over time and were correlated with prescription opioid use or the Medicaid system. Such covariates include overall physician supply, buprenorphine-waivered physician supply, general economic conditions, and concurrent state policies, such as prescription drug monitoring program adoption and mandates, pain clinic regulations, and Medicaid expansions. 95% Confidence intervals were derived from standard errors clustered by state to account for within-state serial correlation in a difference-in-differences design. We performed 2 sets of sensitivity analyses: first, we included group-specific linear trends at the US Census Division level to account for the unobserved US Census Division–wide confounding factors that evolve over time at a constant rate; second, we excluded the states with medical and adult-use marijuana laws in place before 2011 from the comparison states. Furthermore, we performed "parallel-trend assumption" tests by statistically and graphically comparing the prepolicy trends between medical marijuana states, adult-use marijuana states, and the comparison states. We also performed falsification tests by examining the policy effects on 3 classes of drugs prescribed for conditions that were unlikely to be affected by marijuana use or marijuana liberalization policies. These sensitivity analyses and statistically checks can be found in the Supplement.

# Results

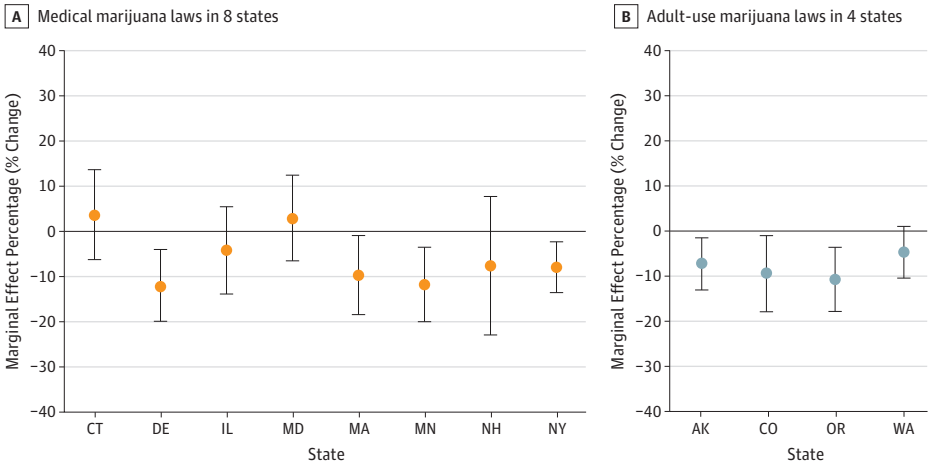
**Figure 1** indicates that state implementation of medical and adult-use marijuana laws was associated with a lower Medicaid-covered opioid prescribing rate. Specifically, the implementation of medical marijuana laws was associated with a 5.88% lower rate of Medicaid-covered prescriptions for all opioids (95% CI, −11.55% to approximately −0.21%). Given that the annual rate of Medicaid-covered opioid prescriptions is on average 670.16 per 1000 enrollees in states without medical marijuana laws, the effect size of medical marijuana laws is equivalent to 39.41 fewer opioid prescriptions per 1000 enrollees per year. Moreover, when states with existing medical marijuana laws implemented adult-use marijuana laws, the implementation of adult-use marijuana laws was associated with an additional 6.38% lower opioid prescription rate (95% CI, −12.20% to approximately −0.56%). Using the annual average in states with medical marijuana laws but no adult-use marijuana laws (ie, 621.82 opioid prescriptions per 1000 enrollees), the effect size of adult-use marijuana laws can be translated to 39.67 fewer

Figure 1. Association Between Medical and Adult-Use Marijuana Laws and Medicaid-Covered Opioid Prescribing Rate




Analysis of the CMS State Drug Utilization Data, 2011-2016.[19] Opioid prescribing rate was measured by the number of Medicaid-covered prescriptions for opioids on a quarterly, per-1000-Medicaid-enrollees basis and was population-weighted. Error bars indicate 95% CIs clustered at the state level. Orange dots indicate prescribing rates under medical marijuana laws; gray dots, rates under adult-use marijuana laws. Rates and 95% CIs are also presented in eTables 3, 5, and 6 in the Supplement.

Figure 2. State-Specific Association Between Medical and Adult-Use Marijuana Laws and Medicaid-Covered Opioid Prescribing Rate




Analysis of the CMS State Drug Utilization Data, 2011-2016.[19] Opioid prescribing rate was measured by the number of Medicaid-covered prescriptions for opioids on a quarterly, per-1000-Medicaid-enrollees basis and was population-weighted. Error bars indicate 95% CIs clustered at the state level. Dots indicate prescribing rates. Rates and 95% CIs are also presented in eTable 4 in the Supplement. AK indicates Alaska; CO, Colorado; CT, Connecticut; DE, Delaware; IL, Illinois; MA, Massachusetts; MD, Maryland; MN, Minnesota; NH, New Hampshire; NY, New York; OR, Oregon; WA, Washington.

opioid prescriptions per 1000 enrollees per year. Furthermore, the estimated lower rate of opioid prescribing associated with adult-use marijuana laws was mainly concentrated in Schedule II opioids (−7.79%; 95% CI, −14.73% to approximately −0.85%), whereas the lower prescribing rate associated with medical marijuana laws was more pronounced in Schedule III to V opioids (−10.40%; 95% CI, −19.05% to approximately −1.74%).

The state-specific policy effects presented in **Figure 2** reveal a more nuanced picture. Among the 8 states that started to implement medical marijuana laws during the study period, Delaware, Massachusetts, Minnesota, and New Hampshire had significant lower opioid prescribing rates, whereas the plausible differences in opioid prescribing rates in Illinois and New Hampshire were not precisely estimated. Connecticut and Maryland, however, did not have clinically meaningful or statistically discernable changes in opioid prescribing rates associated with the implementation of medical marijuana laws.

Regarding the adult-use marijuana states, 3 of the 4 states (ie, Alaska, Colorado, and Oregon) had significantly lower opioid prescribing rates associated with the implementation of adult-use marijuana laws, whereas the change in Washington was relatively moderate.

Furthermore, the implementation of adult-use marijuana laws was associated with a 9.78% lower Medicaid spending on prescription opioids (95% CI, −18.29% to approximately −1.26%), equivalent to an annual saving of $1815 Medicaid spending per 1000 enrollees (**Table**). The implementation of medical and adult-use marijuana laws was also associated with a lower rate of Medicaid-covered prescriptions for nonopioid pain medications of 8.36% (95% CI, −13.67% to approximately −3.05%) and 8.69% (95% CI, −15.50% to approximately −1.89%), respectively (Table).

Results from sensitivity analyses were consistent with the main findings. Moreover, the "parallel-trend assumption" tests and falsification tests lent weight to the validity of the methods (Supplement).

Table. Association Between Medical and Adult-Use Marijuana Laws and Medicaid-Covered Prescribing Rate of and Spending on Pain Medications[a]

| Medication Type | Prescriptions, No. | | Cost, $ | |
|---|---|---|---|---|
| | Relative Change, % (95% CI) | Absolute Annual Effect Size per 1000 Enrollees | Relative Change, % (95% CI) | Absolute Annual Effect Size per 1000 Enrollees |
| All opioid pain medications | | | | |
| Medical marijuana laws | −5.88 (−11.55 to −0.21) | −39.41 | −2.87 (−8.16 to 2.42) | ... |
| Adult-use marijuana laws | −6.38 (−12.20 to −0.56) | −39.67 | −9.78 (−18.29 to −1.26) | −1815.5 |
| Schedule II opioids | | | | |
| Medical marijuana laws | −4.69 (−10.05 to 0.67) | −24.56 | −2.11 (−9.45 to 5.12) | ... |
| Adult-use marijuana laws | −7.79 (−14.73 to −0.85) | −36.48 | −11.93 (−21.26 to −2.60) | −1916.4 |
| Schedule III-V opioids | | | | |
| Medical marijuana laws | −10.40 (−19.05 to −1.74) | −15.14 | −14.27 (−32.20 to 3.75) | ... |
| Adult-use marijuana laws | −1.36 (−12.93 to 10.21) | ... | 0.39 (−8.55 to 9.33) | ... |
| Nonopioid pain medications | | | | |
| Medical marijuana laws | −8.36 (−13.67 to −3.05) | −105.36 | −3.92 (−9.28 to 1.44) | ... |
| Adult-use marijuana laws | −8.69 (−15.50 to −1.89) | −95.65 | −9.85 (−21.85 to 2.15) | ... |

Abbreviation: ellipses, not significant at the .05 level.

[a] Analysis of the Centers for Medicare and Medicaid State Drug Utilization Data, 2011-2016.[19] The opioid prescribing rate was measured by the number of Medicaid-covered prescriptions for opioids and nonopioid pain medications on a quarterly, per-1000-Medicaid-enrollees basis and were population-weighted; the nominal spending values between 2011 and 2016 were converted to real values based on national monthly Consumer Price Index.

## Discussion

This study provides some of the first empirical evidence that the implementation of medical and adult-use marijuana laws from 2011 to 2016 was associated with lower Medicaid-covered opioid prescribing rates and spending. The study findings are consistent with those of Bradford and Bradford,[15,16] who found reductions in broad category of pain prescriptions covered by Medicaid associated with medical marijuana laws. Our focus on opioids specifically is important in the context of the current epidemic. Furthermore, we also found that implementation of adult-use marijuana laws was associated with even lower rates of opioid prescribing, which previously had not been investigated.

Most opioid use disorder and overdose cases occurred in patients with legitimate prescriptions from health care professionals for pain management.[29] Marijuana liberalization, therefore, may have benefited these patients by providing them with legal protection and access to marijuana as an alternative relief from their pain conditions.[7,8] According to the 2017 Yahoo News/Marist Poll,[30] 83% of Americans supported legalizing marijuana for medical purpose. The widespread public support will bring medical marijuana laws to more and more states for years to come, which may help decrease the use of prescription opioids in pain management and the adverse consequences, such as opioid use disorder and overdose. Furthermore, emerging evidence suggests that marijuana may help ease opioid withdrawal symptoms.[31] Thus, marijuana liberalization potentially reduced prescription opioid use on 2 fronts, serving as a substitute for opioid pain medications, and as a complement to opioid use disorder treatment.

When exploring the policy heterogeneity across states, we identified 2 states, Connecticut and Maryland, where the medical marijuana laws had much less effect on opioid prescribing. There are some possible explanations for these 2 notable exceptions. First, Connecticut did not list any pain conditions as eligible conditions for medical marijuana during the study period (included only "complex regional pain syndrome," a very uncommon chronic pain condition, as one of the extended eligible conditions in late 2016). Second, Maryland, despite the law going into effect in June 2014, did not have an operational medical marijuana system in place until late 2016 owing to multiple legal disputes and bureaucratic challenges.

Furthermore, the association between adult-use marijuana laws and lower prescription opioid rate and spending are worth noting. Because states with adult-use marijuana laws all had medical marijuana laws in place before the implementation of adult-use marijuana laws, the further reductions in opioid prescribing associated with the newly implemented adult-use marijuana laws suggest that there were individuals beyond the reach of medical marijuana laws who may also benefit from using marijuana in lieu of opioids. Our finding that the lower opioid prescribing rates associated with adult-use marijuana laws were pronounced in Schedule II opioids, further suggest that reaching these individuals may have greater potential to reduce the adverse consequences, such as opioid use disorder and overdose. The 2017 Gallup Poll shows a record high 64% of Americans in favor of adult-use marijuana laws.[32] Four of the 5 ballot initiatives for adult-use marijuana were passed on the 2016 Election Day alone.[10] In 2018, more states with existing medical marijuana laws may vote on adult-use marijuana bills. The potential of adult-use marijuana laws to reduce the use and consequences of addictive opioids deserves consideration, especially in states that have been hit hard by the opioid epidemic. As for the states currently reluctant to consider the outright legalization of adult-use marijuana and those still debating medical marijuana, policy efforts can still be made in legislation and implementation process to extend the availability of marijuana to more people who may benefit from the therapeutic value of marijuana.

### Limitations

This study is subject to the following limitations. First, the aggregate nature of the study data did not allow us to identify opioid prescriptions for individual Medicaid enrollees or individual patients treated for pain. Thus, we cannot distinguish between changes on the extensive margin (ie, the number of individuals with any opioid prescription) and the changes on the intensive margin (ie, the number of prescriptions to those already been prescribed opioids). Another limitation of this state-level study lies in that inferences about individual-level mechanisms can only be deduced from the inference for states to which the individuals belong. Second, the data lack the necessary information to adjust our measures of prescription counts for the variations in dosage and strength or to convert the prescription counts into more standardized values, such as morphine milligram equivalents. Third, the geographic proximity and cultural similarity between states with medical or adult-use marijuana laws and those without such laws suggests that the laws were not likely to be "randomly assigned" to states. Thus, as with any observational study, we cannot definitively establish causality between marijuana liberalization and opioid prescribing.

## Conclusions

These findings suggest that medical and adult-use marijuana laws have the potential to reduce opioid prescribing for Medicaid enrollees, a segment of population with disproportionately high risk for chronic pain, opioid use disorder, and opioid overdose.[20] Nonetheless, marijuana liberalization alone cannot solve the opioid epidemic. As with other policies evaluated in the previous literature, marijuana liberalization is but one potential aspect of a comprehensive package to tackle the epidemic.[33]


### ARTICLE INFORMATION

**Accepted for Publication:** February 16, 2018.

**Published Online:** April 2, 2018. doi:10.1001/jamainternmed.2018.1007

**Author Contributions:** Both authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Both authors.
*Acquisition, analysis, or interpretation of data:* Both authors.
*Drafting of the manuscript:* Both authors.
*Critical revision of the manuscript for important intellectual content:* Both authors.
*Statistical analysis:* Wen.

**Conflict of Interest Disclosures:** None reported.


### REFERENCES


1. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-1321.

2. Volkow ND. America's addiction to opioids: heroin and prescription drug abuse. Washington, DC: Senate Caucus on International Narcotics Control. May 14, 2014. https://www.drugcaucus.senate.gov/sites/default/files/Volkow%20Testimony.pdf. Accessed July 12, 2017.

3. Dowell D, Zhang K, Noonan RK, Hockenberry JM. Mandatory provider review and pain clinic laws reduce the amounts of opioids prescribed and overdose death rates. *Health Aff (Millwood)*. 2016;35(10):1876-1883.

4. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014;71(7):821-826.

5. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*. 2014;174(10):1668-1673.

6. Wilkinson ST, Yarnell S, Radhakrishnan R, Ball SA, D'Souza DC. Marijuana legalization: impact on physicians and public health. *Annu Rev Med*. 2016;67:453-466.

7. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol*. 2011;72(5):735-744.

8. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA*. 2015;313(24):2474-2483.

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

10. National Conference of State Legislation (NCSL). Deep Dive: Marijuana. Denver, CO: National Conference of State Legislation. 2016. http://www.ncsl.org/bookstore/state-legislatures-magazine/marijuana-deep-dive.aspx. Accessed July 12, 2017.

11. Lynskey MT, Heath AC, Bucholz KK, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA*. 2003;289(4):427-433.

12. Hathaway AD, Comeau NC, Erickson PG. Cannabis normalization and stigma: contemporary practices of moral regulation. *Criminol Crim Justice*. 2011;11(5):451-469. doi.org/10.1177/1748895811415345

13. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. *Drug Alcohol Depend*. 2017;173:144-150.

14. Kim JH, Santaella-Tenorio J, Mauro C, et al. State medical marijuana laws and the prevalence of opioids detected among fatally injured drivers. *Am J Public Health*. 2016;106(11):2032-2037.

15. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare part D. *Health Aff (Millwood)*. 2016;35(7):1230-1236.

16. Bradford AC, Bradford WD. Medical marijuana laws may be associated with a decline in the number of prescriptions for Medicaid enrollees. *Health Aff (Millwood)*. 2017;36(5):945-951.

17. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational cannabis legalization and opioid-related deaths in Colorado, 2000-2015. *Am J Public Health*. 2017;107(11):1827-1829.

18. Castlight Health. The opioid crisis in America's workforce. San Francisco, CA: Castlight Health Inc; 2016. http://content.castlighthealth.com/Opioid-Research-Report_LP.html. Accessed July 12, 2017.

19. Center for Medicaid and CHIP Services. Medicaid drug programs data and resources. Baltimore, MD: Centers for Medicare and Medicaid Services (CMS); 2017. http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/medicaid-drug-programs-data-and-resources.html. Accessed July 12, 2017.

20. Han B, Compton WM, Jones CM, Cai R. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA*. 2015;314(14):1468-1478.

21. Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: lessons learned from OxyContin. *JAMA Psychiatry*. 2015;72(5):424-430.

22. Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.

23. US Department of Veterans Affairs. VA/DoD clinical practice guidelines: management of opioid therapy (OT) for chronic pain. Washington, DC: US Department of Veterans Affairs (VA); 2010. https://www.healthquality.va.gov/guidelines/Pain/cot/. July 12, 2017.

24. Murthy VH. Letter From the Surgeon General. Washington, DC: Office of the Surgeon General, U.S. Department of Health and Human Services (HHS); August 25, 2016. https://turnthetiderx.org/. Accessed July 12, 2017.

25. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624-1645.

**26**. Kuehn BM; FDA committee. FDA committee: more restrictions needed on hydrocodone combination products. *JAMA*. 2013;309(9):862.

**27**. Pacula RL, Powell D, Heaton P, Sevigny EL. Assessing the effects of medical marijuana laws on marijuana use: the devil is in the details. *J Policy Anal Manage*. 2015;34(1):7-31.

**28**. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data*. Cambridge, MA: MIT Press; 2010.

**29**. Volkow ND, McLellan AT. Opioid abuse in chronic pain—misconceptions and mitigation strategies. *N Engl J Med*. 2016;374(13):1253-1263.

**30**. Marist College Institute for Public Opinion. Yahoo News/Marist Poll Weed & the American family. Poughkeepsie, NY: Marist College Institute for Public Opinion; 2017. http://maristpoll.marist.edu/yahoo-newsmarist-poll/. Accessed February 7, 2018.

**31**. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *J Neurosci*. 2009;29(47):14764-14769.

**32**. McCarthy J. Record-high support for legalizing marijuana use in U.S. Washington, DC: Gallup News; 2017. http://news.gallup.com/poll/221018/record-high-support-legalizing-marijuana.aspx. Accessed November 29, 2017.

**33**. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015;36:559-574.

Invited Commentary

# The Role of Cannabis Legalization in the Opioid Crisis

Kevin P. Hill, MD, MHS; Andrew J. Saxon, MD

**The United States remains gripped** by the opioid crisis. Each day, 90 Americans die from opioid overdoses.[1] Owing to the incredible reach of the opioid crisis—it has affected people of every race, sex, and age across our country—many stakeholders are trying to combat the crisis using multipronged approaches emphasizing prevention, treatment, and law enforcement.

In this issue of *JAMA Internal Medicine*, Bradford et al[2] and Wen and Hockenberry[3] report results suggesting that cannabis legalization may play a beneficial role in the opioid crisis. To examine the association between prescribing patterns for opioids in Medicare Part D and the implementation of state medical cannabis laws (MCLs), Bradford et al[2] performed a longitudinal analysis of the number of prescriptions filled under Medicare Part D for all opioids as a group and for the categories of opioids by state and state-level MCLs from 2010 through 2015. Medicare Part D prescriptions for opioids fell by 2.21 million daily doses filled per year (95% CI, −4.15 to −0.27) when MCLs went into effect in a given state. The type of MCL implemented in these states was important as well, with greater reductions in opioid prescriptions observed in states with more structured MCLs that increased access to medical cannabis. Prescriptions for opioids fell by 3.74 million daily doses per year (95% CI, −5.95 to −1.54) when medical cannabis dispensaries opened, but only by 1.79 million daily doses per year (95% CI, −3.36 to −0.22) when states only offered allowances for home cultivation. Similarly, Wen and Hockenberry[3] analyzed Medicaid prescription data from 2011 to 2016 and found that both medical and recreational cannabis laws were associated with annual reductions in opioid prescribing rates of 5.88% and 6.38%, respectively.

Author Audio Interview

Related articles pages 667 and 673

These investigations, while novel, had several important limitations. First, they are ecologic analyses: we do not know whether patients actually avoided or reduced opioid use because of increased access to cannabis. Although the analyses controlled for several important state-specific variables, there are a multitude of other factors that may affect the association between medical cannabis and opioids in a given state and that are known to be associated with regional variation in opioid prescribing that were not adjusted for such as racial composition, educational attainment, prevalence of disease, disability, and suicide rates.[3] Finally, conclusions drawn from Medicare Part D or Medicaid data, which include primarily disabled individuals, individuals 65 years or older, and others with low income levels, such as families, children, or pregnant women, may not be generalizable to other demographic groups.

Nevertheless, these results do dovetail with preclinical research showing that cannabinoid and opioid receptor systems mediate common signaling pathways central to clinical issues of tolerance, dependence, and addiction. These concepts support anecdotal evidence from patients who describe a decreased need for opioids to treat chronic pain after initiation of medical cannabis pharmacotherapy. The current investigations by Bradford et al and Wen and Hockenberry also build on other evidence derived from administrative data sets suggesting that implementing medical cannabis or recreational cannabis policies may be associated with reduced opioid use and mortality. Bachhuber et al[4] used a time series analysis of MCLs and state-level death certificate data in the United States from 1999 to 2010 to examine the association between the presence of state MCLs and opioid analgesic overdose mortality. They found that states with MCLs had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; $P$ = .003) compared with states without MCLs. Finally, Livingston et al[5] compared changes in monthly opioid-related deaths before and after Colorado stores began selling recreational cannabis and found that legalization of recreational cannabis sales and use resulted in a 0.7 per month (β = −0.68; 95% CI, −1.34 to −0.03) reduction in opioid-related deaths.

Not all studies, however, find that cannabis supplants opioid use. For example, Olfson et al[6] used the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data set to assess prospective associations between cannabis use and subsequent opioid use. Their analysis showed that cannabis use was associated with increased incident nonmedical prescription opioid use (odds ratio, 5.78; 95% CI, 4.23-7.90) and opioid use disorder (odds ratio, 7.76; 95% CI, 4.95-12.2) at follow-up.

# REFERENCE #3

Lucas *Harm Reduction Journal* (2017) 14:58
DOI 10.1186/s12954-017-0183-9

Harm Reduction Journal

COMMENTARY Open Access

# Rationale for cannabis-based interventions in the opioid overdose crisis

Philippe Lucas[1,2,3]

## Abstract

**Background:** North America is currently in the grips of a crisis rooted in the use of licit and illicit opioid-based analgesics. Drug overdose is the leading cause of accidental death in Canada and the US, and the growing toll of opioid-related morbidity and mortality requires a diversity of novel therapeutic and harm reduction-based interventions. Research suggests that increasing adult access to both medical and recreational cannabis has significant positive impacts on public health and safety as a result of *substitution effect*. Observational and epidemiological studies have found that medical cannabis programs are associated with a reduction in the use of opioids and associated morbidity and mortality.

**Aims and Methods:** This paper presents an evidence-based rationale for cannabis-based interventions in the opioid overdose crisis informed by research on *substitution effect,* proposing three important windows of opportunity for cannabis for therapeutic purposes (CTP) to play a role in reducing opioid use and interrupting the cycle towards opioid use disorder: 1) prior to opioid introduction in the treatment of chronic pain; 2) as an opioid reduction strategy for those patients already using opioids; and 3) as an adjunct therapy to methadone or suboxone treatment in order to increase treatment success rates. The commentary explores potential obstacles and limitations to these proposed interventions, and as well as strategies to monitor their impact on public health and safety.

**Conclusion:** The growing body of research supporting the medical use of cannabis as an adjunct or substitute for opioids creates an evidence-based rationale for governments, health care providers, and academic researchers to consider the implementation and assessment of cannabis-based interventions in the opioid crisis.

**Keywords:** Addiction, Opioids, Cannabis, Marijuana, Substitution, Harm reduction

## Background

North America is currently in the grips of a crisis rooted in the use of licit and illicit opioid-based analgesics. Drug overdose is the leading cause of accidental death in Canada and the US, with many of these deaths amongst people affected by opioid use disorder. In 2015, there were 52,404 drug overdose deaths in the US, including 33,091 (63.1%) overdose deaths related to opioids [1]. In British Columbia, despite the declaration of a public health emergency in 2016 and the scale-up of public health-based efforts such as the opening of emergency overdose prevention sites in many high-use jurisdictions, use and overdose rates continue to rise. On April 26th British Columbia reported 130 opioid-related overdoses emergency calls in a single day,[1] and in March 2017, 120 individuals died of drug overdoses.[2] In light of the growing toll of opioid-based morbidity and mortality, this crisis requires a diversity of novel therapeutic and harm reduction-based interventions, and evidence suggests cannabis may have a role to play in reducing some of these harms.

### Substitution effect

Substitution effect is a theory originating from behavioral economics that examines how the availability of one good can impact and influence the use of other

Correspondence: plucas@uvic.ca
[1]Graduate Researcher, Centre for Addictions Research of British Columbia, 2300 McKenzie Ave, Victoria, BC V8N 5M8, Canada
[2]Social Dimensions of Health, University of Victoria, 3800 Finnerty Rd, Victoria, BC V8P 5C2, Canada
Full list of author information is available at the end of the article

goods. In regards to substance use, Hursh et al. (2005) suggest that "pharmacological therapies for the treatment of drug abuse can also be conceptualized 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)" [2]. Common examples of such harm reduction-focused substitution effect include the use of e-cigs or nicotine patches as alternatives to cigarettes, or methadone/suboxone treatment as an alternative to heroin. This paper presents an evidence-based rationale for cannabis-based interventions in the opioid overdose crisis informed by research on *substitution effect* and the principles of harm reduction.

There is a growing amount of evidence that increasing adult access to both medical and recreational cannabis has significant positive impacts on public health and safety, largely as a result of substitution effect. Population-level research describes how the introduction of regimes for legal access to cannabis (e.g., medical and/or recreational) in some US states has preceded reductions in homicides and violent crime [3], suicides [4], and automobile-related fatalities [5–7], all potentially related to subsequent declines in alcohol use. Additionally, epidemiological research has found that medical cannabis programs are associated with a reduction in the use of opioids and associated morbidity and mortality. Bachhuber et al. [8] report that U.S. states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared to states without medical cannabis laws, and a 2016 study found that the number of Medicare prescriptions to seniors in medical cannabis states dropped for drugs that treat pain, depression, anxiety, nausea, psychoses, seizures and sleep disorders [9]. For pain, the annual number of annual doses prescribed per physician fell by 1826 doses. More recently, a retrospective survey of Michigan patients concluded that medical cannabis use was associated with a 64% decrease in opioid use ($n$ = 118), decreased side effects of medications, and an improved quality of life [10], and a large survey of 2897 medical cannabis patients in California found that 30% of the sample ($n$ = 841) reported using opioid-based pain medications, 97% of which "strongly agreed/agreed" that they were able to decrease their opioid use when using medical cannabis [11].

A 2015 cross sectional survey of patients in Canada's national medical cannabis system found that 63% of respondents reported substituting cannabis for prescription drugs ($n$ = 166), with 32% of the pharmaceuticals being substituted for being prescription opioids ($n$ = 80). The primary reasons cited by patients for this substitution were "less adverse side effect" (39%, $n$ = 68); "cannabis is safer" (27%, $n$ = 48), and "better symptom management" (16%, $n$ = 28) [12]. This evidence is consistent with information from Veteran's Affairs Canada (VAC) showing that a recent significant increase in the use of medical cannabis by Canadian veterans was paralleled by a reduction of approximately 30% in the number of prescriptions for benzodiazepines, and a 16% decrease in the use of opioids [13].

Research suggests that there are multiple mechanisms of action that may result in the substitution of cannabis for opioids. In a study of cannabinoid-opioid interactions, Abrams et al. (2011) note that cannabinoids and opioids share many similar therapeutic and pharmacodynamics properties, including analgesic effects; the potential to induce hypothermia, sedation, and hypotension; as well as inhibition of intestinal motility and locomotor activity [14], adding that

> "Synergy in analgesic effects between opioids and cannabinoids has been demonstrated in animal models. The antinociceptive effects of morphine are mediated predominantly by mu opioid receptors but may be enhanced by delta-9-tetrahydrocannabinol (THC) activation of kappa and delta opiate receptors [15]. It has further been suggested that the cannabinoid–opioid interaction may occur at the level of their signal transduction mechanisms [16, 17]. Receptors for both classes of drugs are coupled to similar intracellular signaling mechanisms that lead to a decrease in cyclic adenosine monophosphate production via G protein activation [17–19]. There is also some evidence that cannabinoids increase the synthesis and/or release of endogenous opioids." (p. 844)

In light of the growing overdose crisis in North America, these findings on cannabis substitution effect and the biological mechanisms behind it strongly suggest that cannabis could play a role in reducing the public health impacts of prescription and non-prescription opioids. However, interventions testing the harm reduction potential of cannabis substitution effect have been lacking thus far. The following framework describes how novel cannabis-based interventions could minimize the personal and social harms associated with opioids.

## Methods

A compelling amount of evidence suggests there may be specific windows of opportunity for cannabis for therapeutic purposes (CTP) to play a role in the opioid use and dependence cycle. This commentary synthesizes the growing amount of research on cannabis substitution effect into specific policy recommendations aimed at improving public health and safety outcomes, with a focus on the 3 primary opportunities for cannabis to potentially reduce opioid use disorder and associated morbidity and mortality: 1) prior to opioid introduction

in the treatment of chronic pain; 2) as an opioid reduction strategy for those already using opioids; and 3) as an adjunct therapy to methadone or Suboxone treatment in order to increase treatment success rates.

### Introduction/initiation

The pathway to opioid use disorder typically begins with the use of pharmaceutical opioids. Research suggests that 4 out of 5 heroin users report their opioid use began with prescription opioids [20]. If physicians and patients have access to a safer, less addictive alternative for pain control like cannabis [21], introducing it into the course of care as a first line treatment could potentially prevent the opioid overuse cycle from starting by not only reducing the risk pain patients would have of developing opioid use disorders, but also by reducing the overall supply of pharmaceutical opioids on the black market.

Clinical research on cannabis as a treatment for pain is extensive and suggests a relatively safe and effective treatment option [14, 22–26], and there is significant population-level evidence that cannabis substitution for opioids in the treatment of chronic pain is already taking place throughout North America. Chronic pain is the most common indication reported by Canadian and US patients who use medical cannabis [10, 27], and epidemiological studies by Bachhuber et al. [8] and Bradford and Bradford [9] strongly suggest that access to medical cannabis through state-level programs in the US reduces opioid use and related harms.

In light of this data, it would seem logical to seek to develop policies and associated education strategies to increase physician support for CTP in the treatment of chronic pain, and thereby reduce the health care provider community's dependence on opioids as first or second line treatments options. However, while opioids remain second line treatment options throughout North America, clinical guidelines in Canada designate cannabis a third or fourth line treatment option for pain, and in the US, federal prohibition on the medical use of cannabis means that in many states, this is not an available treatment option under any circumstance.

It has become apparent that Canadian clinical guidelines and the US's national prohibitionist policies are no longer reflective of the most current evidence and best available science on cannabis, opioids, and the treatment of chronic pain, and may in fact be inadvertently contributing to the growing rate of opioid use disorder. The growing body of research on the impact of cannabis on the use of other, potentially more dangerous substances creates a strong rationale to review these policies through a public health centered lens informed by the ongoing and increasing detrimental impacts of the current opioid crisis.

The argument in favor of recognizing medical cannabis as a first line option in the treatment of chronic pain is informed by science, common sense, and simple compassion: if patients never start using opioids, there is no risk their use might progress to dependence or overdose.

### Reduction/substitution

For those patients that are already using opioids in their course of care, the therapeutic imperative is to ensure treatment success without a progression to dependence and/or overuse. Evidence suggests that cannabis can be a useful adjunct therapy in meeting these goals. Cannabis augments the pain relieving potential of opioids [14], and can re-potentiate their effects [28], thereby reducing the need to increase the dosage of opioid pain medications. As noted earlier, cross-sectional and population-level research has shown that introducing cannabis into the treatment of chronic pain may result in a reduction or complete cessation of opioid use [11, 12, 29–33], thereby significantly reducing the potential for dependence or overdose. These findings suggest an opportunity to reduce opioid use through the development of therapeutic guidelines to safely introduce medical cannabis as an adjunct therapy for patients using opioids in the treatment of chronic pain. The aim of this strategy would be to slowly introduce cannabis into the continuum of care, while subsequently reducing the dosage and frequency of prescription opioid use.

However, here too there are some possible obstacles to implementation. Many members of the health care community and their respective organizations have expressed concerns about the use of medical cannabis, with much of the focus centering on smoking as a mode of use, and the impact of cannabis use on potentially vulnerable populations.

In regards to concerns over smoking as a route of administration, research suggests those who smoke cannabis regularly may be at increased risk of bronchial issues, however no causal link between cannabis use and lung or upper respiratory cancer has ever been established [34]. Encouragingly, recent patient surveys have found that alternatives to smoking such as vaporization and edibles are increasingly popular amongst patient and recreational populations [35, 36], and a 2015 survey of Canadian medical cannabis patients found that over 50% of patients report non-smoked options as their primary method of use [12]. Additionally, in Canada the availability of high quality oil-based extracts (e.g., drops and capsules) through the federal Access to Cannabis for Medical Purposes Regulations (ACMPR) provides patients and health care practitioners with legal, standardized alternatives to smoked ingestion. However, any cannabis-based medical intervention should be coupled

with an educational campaign to discourage smoking and inform patients and physicians of safer alternative methods of use.

In regards to vulnerable populations, it's certainly true that due to circumstances or pre-existing medical conditions, so individuals may not be well suited for cannabis-based therapies. In particular, a recent systematic review of medical cannabis and mental health suggests that "CTP users with psychotic disorders, and those at increased genetic risk of developing such disorders, should be cautioned regarding the use of cannabis" [37]. However, the same review also noted that medical cannabis may be useful in the treatment of post-traumatic stress disorder (often a co-morbidity with substance use issues), and that its use is not associated with increased violence. In fact, a 2014 study found that cannabis use resulted in reductions in interpersonal violence amongst married couples [38].

Other potentially vulnerable populations include youth and women who may be pregnant, and as with many currently available prescription drugs – including opioids - physicians should carefully weigh the potential harms and benefits of cannabis treatment when treating these populations.

Additionally, cannabis that is high in cannabidiol (CBD) and low in tetrahydrocannabinol (THC) may reduce potential harms to vulnerable populations. CBD is a relatively safe, non-impairing cannabinoid that has been shown to have many therapeutic effects relevant to the opioid crisis, including the reduction of heroin-seeking behavior in mice [39], and positive effects on mental health conditions like anxiety, depression, psychosis and bi-polar disorder [37, 40]. In other words, the existence of vulnerable populations should not result in abandoning or otherwise withholding this treatment option from others who might benefit from CTP, particularly in the treatment of chronic pain. It does however highlight the need to target outreach and education campaigns and specific treatment modalities aimed at reducing potential cannabis-related harms to these vulnerable populations.

### Replacement/Cessation

When opioid use graduates to dependence, it is imperative that users seeking opioid replacement therapy (ORT) enjoy the best possible chance of success, and some research has found that cannabis use can positively impact treatment success rates. For example, intermittent cannabis users showed superior retention in naltrexone treatment compared to abstinent or consistent users [41]. Additionally, objective ratings of opioid withdrawal decreased in patients concurrently using cannabis during the early stages of methadone stabilization [42], and CBD has been shown to reduce heroin seeking behavior in mice [39].

Greater ORT success rates reduce the risk of those with opioid use disorder suffering a relapse and subsequent fatal overdose, thereby diminishing the health care and public safety cost burden for all members of society. Since there is an exceedingly high risk of relapse and overdose in this dependent population [42, 43] - particularly with introduction of fentanyl and other powerful opioids into the illicit drug market - systematic research-based strategies to explore the potential of medical cannabis to improve ORT success rates should be implemented immediately. In order to address the need for good longitudinal data on the impact of cannabis-based medicines on methadone/Suboxone treatment, I have worked with Dr. Peter Farago to develop a multi-site cohort study that will compare the success rate of ORT in 250 cannabis using patients vs. 250 non-cannabis using controls. The study received ethics approval in May 2017 and will launch summer/fall 2017.

Patients seeking treatment for opioid use disorder deserve the best possible chance of success. Since evidence suggests that cannabis can help reduce opioid cravings and subsequently improve treatment retention and compliance, there is a strong rationale to immediately proceed with this novel intervention and associated studies.

### Implementation and assessment

It is notable that many of the favorable cannabis-related public health outcomes cited in this commentary did not come about as a result of a deliberate strategy to substitute cannabis for opioids, but rather through unintentional in situ changes in patient behavior resulting from cannabis use. This strongly suggests that a more purposeful and strategic approach to cannabis substitution for opioids may lead to even more encouraging outcomes, and Canada may be particularly well positioned to implement these proposed interventions. With a long-standing federally regulated medical cannabis program that currently serves over 150,000 Canadians with physician support for medical cannabis, and access to quality-tested medical cannabis products labeled for THC and CBD content, outreach and education to health care practitioners touting the three opportunities for cannabis-based interventions could be accomplished very quickly, and could thereby have nearly immediate impacts on opioid use.

Of interest in regards to the assessment and evaluation of these public policy measures, a number of provinces have centralized tracking of prescription drug dispensing, so detailed real-time data on the use of prescription opioids would be available to measure the population-level impacts of these interventions. This data could be coupled with well-designed epidemiological studies tracking overdose

rates through first responder calls and emergency room data, as well as prospective observational cohort studies comparing methadone/suboxone treatment success rates in cannabis and non-cannabis using populations.

Observational and epidemiological research would not replace the need for high quality clinical trials examining the impact of cannabis on chronic pain, opioid use, and quality of life. Well-designed clinical trials continue to be necessary studies to determine the most effective method of use (inhalation or oral ingestion), optimal chemical composition (THC and CBD ratios and overall potency), and associated dosage to most effectively impact opioid use in all 3 of the proposed interventions. However, the significant public health impact of the current opioid crisis merits a rapid response strategy, and Canada's federal Access to Cannabis for Medical Purposes Regulations and associated supply of cannabis and cannabis-based medications would allow for rapid implementation in a responsible and reflexive manner informed by existing regional, provincial and national pharmacovigilance and outcome assessment programs.

## Conclusion

Bureaucratic, legal and ideological obstacles to these interventions unquestionably exist in some jurisdictions. However, t is encouraging to see acknowledgements of the potential impacts of medical cannabis on opioid use from traditionally conservative organizations like the National Institute on Drug Abuse (NIDA), which recently acknowledged the growing scientific support for substitution effect on its website, noting that while "research into the effects of cannabis on opioid use in pain patients is limited…data suggest that medical cannabis treatment may reduce the dose of opioids required for pain relief".[3]

Cannabis alone will not end opioid use disorder and associated morbidities and mortality. However, the introduction of ever more powerful opioids like fentanyl and carfentanyl into the illicit drug market and the resulting day-to-day increase in opioid overdoses highlights the immediate need for innovative short and long term intervention strategies to add to current efforts like ORT, heroin maintenance programs, supervised consumption sites, the depenalization of substance use, and increased education and outreach on the potential harms associated with both prescription and illicit opioid use. The growing body of research supporting the medical use of cannabis as an adjunct or substitute for opioids creates an evidence-based rationale for governments, health care providers, and academic researchers to seek the immediate implementation of cannabis-based interventions in the opioid crisis at the regional and national level, and to subsequently assess their potential impacts on public health and safety.

## Endnotes

[1]Matt Meuse, April 27, 2017. B.C. breaks record for daily overdose ambulance calls. CBC News.

[2]Staff, April 19th, 2,017,120 died in B.C. last month of illicit overdoses. Global News. http://globalnews.ca/news/3389500/120-died-in-b-c-last-month-of-illicit-overdoses/

[3]https://www.drugabuse.gov/publications/marijuana/marijuana-safe-effective-medicine

#### Acknowledgements
The author would like to thank and acknowledge M-J Milloy PhD and Zach Walsh PhD for their useful suggestions and feedback on this article.

#### Funding
No funding was necessary for the production of this Commentary.

#### Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

#### Authors' contributions
PL conceptualized and wrote this article. M-JM and ZW provided feedback on the manuscript, and their contributions are are recognized in the acknowledgements.

#### Ethics approval and consent to participate
N/A

#### Consent for publication
N/A

#### Competing interests
Philippe Lucas is VP, Patient Research & Access for Tilray, a federally authorized medical cannabis production and research company located in Nanaimo, British Columbia. He is paid a salary for this employment, and holds stock options in Privateer Holdings, the owner of Tilray.

## Publisher's Note



#### Author details
[1]Graduate Researcher, Centre for Addictions Research of British Columbia, 2300 McKenzie Ave, Victoria, BC V8N 5M8, Canada. [2]Social Dimensions of Health, University of Victoria, 3800 Finnerty Rd, Victoria, BC V8P 5C2, Canada. [3]VP, Patient Research & Access, Tilray, 1100 Maughan Rd, Nanaimo, BC V9X1J2, Canada.

Received: 19 June 2017 Accepted: 9 August 2017
Published online: 18 August 2017

#### References

1. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep. 2016;65:1445–52. doi:10.15585/mmwr.mm655051e1.
2. Hursh SR, Galuska CM, Winger G, Woods JH. The economics of drug abuse: a quantitative assessment of drug demand. Mol Interv. 2005;5:20–8.
3. Morris RG, TenEyck M, Barnes JC, Kovandzic T V. The effect of medical marijuana laws on crime: Evidence from state panel data, 1990–2006. PLoS One. 2014;9:1–7.
4. Anderson DM, Rees DI, Sabia JJ. Medical Marijuana Laws and Suicides by Gender and Age. Am J Public Health. 2014;104:2369–76. doi:10.2105/AJPH.2013.301612.
5. Anderson DM, Hansen B, Rees DI. Medical marijuana laws, traffic fatalities, and alcohol consumption. J Law Econ. 2013;56:333–69. doi:10.1086/668812.
6. Santaella-Tenorio J, Mauro CM, Wall MM, Kim JH, Cerdá M, Keyes KM, et al. US Traffic Fatalities, 1985–2014, and Their Relationship to Medical Marijuana Laws. Am J Public Health. 2017;107:336–42. doi:10.2105/AJPH.2016.303577.

7. Declues K, Perez S, Figueroa A. A 2-Year Study of Δ 9-tetrahydrocannabinol Concentrations in Drivers: Examining Driving and Field Sobriety Test Performance. J Forensic Sci. 2016; doi:10.1111/1556-4029.13168.
8. Bachhuber MA, Salone B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. JAMA Intern Med. 2014;(19104):1–6.
9. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in medicare part d. Health Aff. 2016;35:1230–6.
10. Boehnke KF, Litinas E, Clauw DJ, Arnold LM, Clauw DJ, Dunegan LJ, et al. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016;17:739–44. doi:10.1016/j.jpain.2016.03.002.
11. Reiman A, Welty M, Solomon P. Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report. Cannabis Cannabinoid Res. 2017;2:160–6. doi:10.1089/can.2017.0012.
12. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. Int J Drug Policy. 2017;42:30–5. doi:10.1016/j.drugpo.2017.01.011.
13. Hager M. Among veterans, opioid prescription requests down in step with rise in medical pot. Globe Mail. 2016. http://www.theglobeandmail.com/news/national/among-veterans-opioid-prescription-requests-down-in-step-with-rise-in-medical-pot/article30285591/. Accessed 14 Aug. 2017.
14. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther. 2011;90:844–51. doi:10.1038/clpt.2011.188.
15. Pugh G, Smith PB, Dombrowski DS, Welch SP. The role of endogenous opioids in enhancing the antinociception produced by the combination of delta 9-tetrahydrocannabinol and morphine in the spinal cord. J Pharmacol Exp Ther. 1996;279. https://www.ncbi.nlm.nih.gov/pubmed/8930163. Accessed 10 May 2017.
16. Welch SP, Stevens DL. Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine, in mice. J Pharmacol Exp Ther. 1992;262:10–8. http://www.ncbi.nlm.nih.gov/pubmed/1320680. Accessed 10 May 2017.
17. Welch SP, Eads M. Synergistic interactions of endogenous opioids and cannabinoid systems. Brain Res. 1999;848:183–90. http://www.ncbi.nlm.nih.gov/pubmed/10612710 . Accessed 10 May 2017.
18. Welch SP, Thomas C, Patrick GS. Modulation of cannabinoid-induced antinociception after intracerebroventricular versus intrathecal administration to mice: possible mechanisms for interaction with morphine. J Pharmacol Exp Ther. 1995;272:310–21. http://www.ncbi.nlm.nih.gov/pubmed/7815346 . Accessed 10 May 2017.
19. Pugh G, Welch SP, Bass PP. Modulation of free intracellular calcium and cAMP by morphine and cannabinoids, alone and in combination in mouse brain and spinal cord synaptosomes. Pharmacol Biochem Behav. 1994;49:1093–100. http://www.ncbi.nlm.nih.gov/pubmed/7886081. Accessed 10 May 2017.
20. Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, et al. The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. Annu Rev Public Health. 2015;36:559–74. doi:10.1146/annurev-publhealth-031914-122957.
21. Nutt DJ, King LA, Phillips LD. Drug harms in the UK: A multicriteria decision analysis. Lancet. 2010;376:1558–65.
22. Russo EB. Cannabinoids in the management of difficult to treat pain. Ther Clin Risk Manag. 2008;4:245–59.
23. Jensen B, Chen J, Furnish T, Wallace M. Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence. Curr Pain Headache Rep. 2015;19:50. doi:10.1007/s11916-015-0524-x.
24. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. Neurology. 2007;68:515–21. doi:10.1212/01.wnl.0000253187.66183.9c.
25. Ware MA, Wang T, Shapiro S, Collet J-P. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015; doi:10.1016/j.jpain.2015.07.014.
26. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. CMAJ. 2010;182:1–8.
27. Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, Lucas P, et al. Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. Int J Drug Policy. 2013;24:511–6. doi:10.1016/j.drugpo.2013.08.010.
28. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. Life Sci. 2004;74:1317–24. doi:10.1016/j.lfs.2003.09.038.
29. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016;17:739–44. doi:10.1016/j.jpain.2016.03.002.
30. Lucas P, Walsh Z, Crosby K, Callaway R, Belle-Isle L, Kay R, et al. Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors. Drug Alcohol Rev. 2016;35(3):326–33. doi:10.1111/dar.12323.
31. Lucas P, Reiman A, Earleywine M, McGowan SK, Oleson M, Coward MP, et al. Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey of substitution effect in Canadian medical cannabis patients. Addict Res Theory. 2013;21:435–42. doi:10.3109/16066359.2012.733465.
32. Corroon J, Mischley L, Sexton M. Cannabis as a substitute for prescription drugs – a cross-sectional study. J Pain Res. 2017;10:989–98. doi:10.2147/JPR.S134330.
33. Reiman AE. Self-efficacy, social support and service integration at medical cannabis facilities in the San Francisco Bay area of California. Health Soc Care Community. 2008;16:31–41.
34. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case–control study. Cancer Epidemiol Biomark Prev. 2006;15:1829–34.
35. Hazekamp A, Ware MA, Muller-Vahl K, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—An international cross-sectional survey on administration forms. J Psychoactive Drugs. 2013;45:199–210.
36. Cuttler C, Mischley LK, Sexton M. Sex Differences in Cannabis Use and Effects: A Cross-Sectional Survey of Cannabis Users. Cannabis Cannabinoid Res. 2016;1:166–75. doi:10.1089/can.2016.0010.
37. Walsh Z, Gonzalez R, Crosby K, Thiessen M S, Carroll C, Bonn-Miller MO. Medical cannabis and mental health: A guided systematic review. Clin Psychol Rev. 2017;51:15–29.
38. Smith PH, Homish GG, Collins RL, Giovino GA, White HR, Leonard KE. Couples' marijuana use is inversely related to their intimate partner violence over the first 9 years of marriage. Psychol Addict Behav. 2014;28:734–42. doi:10.1037/a0037302.
39. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J Neurosci. 2009;29:14764–9. doi:10.1523/JNEUROSCI.4291-09.2009.
40. Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res. 2017;2:139–54. doi:10.1089/can.2016.0034.
41. Raby WN, Carpenter KM, Rothenberg J, Brooks AC, Jiang H, Sullivan M, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. Am J Addict. 2009;18:301–8. doi:10.1080/10550490902927785.
42. Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. Am J Addict. 2013;22:344–51.
43. Elkader AK, Brands B, Callaghan R, Sproule BA. Exploring the relationship between perceived inter-dose opioid withdrawal and patient characteristics in methadone maintenance treatment. Drug Alcohol Depend. 2009;105:209–14. doi:10.1016/j.drugalcdep.2009.07.003.

# REFERENCE #4

(PDF was not submitted)

# REFERENCE #5

(PDF was not submitted)

# REFERENCE #6

(PDF was not submitted)

# REFERENCE #7

(PDF was not submitted)

# REFERENCE #8

(PDF was not submitted)

# REFERENCE #9

Published in final edited form as:
*Drug Alcohol Depend*. 2009 November 1; 105(1-2): 154–159. doi:10.1016/j.drugalcdep.2009.07.001.

# Concurrent Validation of the Clinical Opiate Withdrawal Scale (COWS) and Single-Item Indices against the Clinical Institute Narcotic Assessment (CINA) Opioid Withdrawal Instrument

**D. Andrew Tompkins, M.D.**[1], **George E. Bigelow, Ph.D.**[1], **Joseph A. Harrison, B.S.**[1], **Rolley E. Johnson, Pharm.D.**[1,2], **Paul J. Fudala, Ph.D.**[2], and **Eric C. Strain, M.D.**[1]

[1]Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Behavioral Pharmacology Research Unit, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA

[2]Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA, 23235, USA

## Abstract

**Introduction—**The Clinical Opiate Withdrawal Scale (COWS) is an 11-item clinician-administered scale assessing opioid withdrawal. Though commonly used in clinical practice, it has not been systematically validated. The present study validated the COWS in comparison to the validated Clinical Institute Narcotic Assessment (CINA) scale.

**Method—**Opioid-dependent volunteers were enrolled in a residential trial and stabilized on morphine 30 mg given subcutaneously four times daily. Subjects then underwent double-blind, randomized challenges of intramuscularly administered placebo and naloxone (0.4 mg) on separate days, during which the COWS, CINA, and visual analog scale (VAS) assessments were concurrently obtained. Subjects completing both challenges were included (N=46). Correlations between mean peak COWS and CINA scores as well as self-report VAS questions were calculated.

**Results—**Mean peak COWS and CINA scores of 7.6 and 24.4, respectively, occurred on average 30 minutes post-injection of naloxone. Mean COWS and CINA scores 30 minutes after placebo injection were 1.3 and 18.9, respectively. The Pearson correlation coefficient for peak COWS and CINA scores during the naloxone challenge session was 0.85 ($p<0.001$). Peak COWS scores also correlated well with peak VAS self-report scores of bad drug effect ($r=0.57$, $p<0.001$) and feeling sick ($r=0.57$, $p<0.001$), providing additional evidence of concurrent validity. Placebo was not associated with any significant elevation of COWS, CINA, or VAS scores, indicating discriminant validity. Cronbach's alpha for the COWS was 0.78, indicating good internal consistency (reliability).



Corresponding author: D. Andrew Tompkins, M.D. Johns Hopkins University School of Medicine Behavioral Pharmacology Research Unit 5510 Nathan Shock Drive Baltimore, MD 21224 dtompki1@jhmi.edu Office: 410-550-5953 Fax: 410-550-0030.

**Contributors:** All authors have contributed to and approved the final manuscript. Dr. Tompkins wrote the first draft of the manuscript, contributed to interpreting data analysis and assisted in editing. Dr. Bigelow assisted in protocol development, interpreting data analyses, writing, and editing paper. Mr. Harrison conducted research, assisted in protocol development and manuscript editing. Drs. Johnson and Fudala assisted in protocol design and editing the manuscript. Dr. Strain assisted in protocol design, study execution, supervision, writing, and editing the manuscript.

**Conflict of Interest:** Drs. Tompkins and Bigelow as well as Mr. Harrison have no conflict of interest to report. Drs. Johnson and Fudala are employees of Reckitt Benckiser Pharmaceuticals Inc., which is a maker of buprenorphine and provided the funding and medications for the clinical trial. Dr. Strain also is a paid consultant to Reckitt Benckiser Pharmaceuticals. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

**Discussion—**COWS, CINA, and certain VAS items are all valid measurement tools for acute opiate withdrawal.

### Keywords

opioid withdrawal; opioid dependence; Clinical Opiate Withdrawal Scale; Clinical Institute Narcotic Assessment; naloxone; precipitated withdrawal

## 1. Introduction

The opiate withdrawal syndrome, a constellation of characteristic signs and symptoms, has been called “one of the most stereotyped syndromes in clinical medicine” (Isbell, 1950). The first instrument to quantitatively measure withdrawal was developed by Kolb and Himmelsbach in the mid-1930s (Kolb and Himmelsbach, 1938). That scale was based on clinical observations and was weighted heavily towards physical signs of withdrawal, such as systolic blood pressure changes, mydriasis, fever, and respiratory rate changes. In the 1960s, the Opiate Withdrawal Experience Scale, a subset of self-report questions from the Addiction Research Center Inventory (ARCI), was used to quantify the subjective symptoms of withdrawal (Haertzen and Meketon, 1968). However, this scale was time consuming for subjects to complete, even with the derived short form Opiate Withdrawal Questionnaire (Haertzen et al., 1970).

Following development of those initial instruments, multiple other subjective and objective scales have been developed and used (Handelsman et al., 1987; Judson et al., 1980; Wang et al., 1974; Bradley et al., 1987; Gossop, 1990). Methods for using these scales have sought to improve on sensitivity and specificity for detecting withdrawal by controlling the level of physical dependence, the time point within the withdrawal syndrome when the assessment is made, and the possibility of feigned responses. In 1988, Peachey and Lei reported on the reliability and validity of the Clinical Institute Narcotic Assessment (CINA), one of the first scales to include both opiate withdrawal signs and symptoms (Peachey and Lei, 1988). This scale was validated using a naloxone challenge in heroin-dependent subjects and the peak score was found to predict the clinically determined maintenance methadone dose used to treat these patients. However, the CINA required nursing support to measure heart rate and blood pressure and contained items which could be easily feigned. As well, there was no fixed upper limit to the scale given the variable contribution of blood pressure and pulse ratings.

Wesson and colleagues, therefore, developed the Clinical Opiate Withdrawal Scale (COWS). This scale was designed to be administered quickly, was intended to improve upon existing measurement tools, and was first published in a training manual for buprenorphine treatment (Wesson et al., 1999). The COWS consisted of an 11-item rating system that could be completed within two minutes by a trained observer and could track opioid withdrawal as differentiated from opioid toxicity through serial measurements. Total scores ranged from 0 to 47, and withdrawal was classified as mild (5-12), moderate (13-24), moderately severe (25-36), or severe (>36). These category scores were not derived using standard statistical techniques but were based upon the authors’ clinical expertise (Wesson and Ling, 2003). Because of its clinical utility, its association with buprenorphine maintenance, and ease of application, the COWS has become widely used for assessing opiate withdrawal (Center for Substance Abuse Treatment, 2004). Although the scale was modeled after items on previously validated scales, the COWS itself has never been systematically validated (Wesson and Ling, 2003). The present project assessed the validity of the COWS in comparison to a previously validated instrument, the CINA, using a double-blind, placebo-controlled naloxone challenge in opioid-dependent individuals. As well, comparisons between the COWS, CINA, and single-

item subjective ratings (Visual Analogue Scales) were done to examine the validity and possible utility of using one overall item to assess opioid withdrawal.

## 2 Methods

### 2.1 Participants

Forty-six out-of-treatment opioid-dependent volunteers participated while residing on a supervised research unit at the Johns Hopkins Behavioral Pharmacology Research Unit (BPRU). Participants were recruited for a clinical trial that will be reported on separately; the trial was registered at www.clinicaltrials.gov, identifier NCT00637000. The analyses in this paper were done as part of the confirmation of opioid physical dependence required for the subsequent opioid clinical pharmacology study. In order to be enrolled, participants had to meet DSM-IV-TR (American Psychiatric Association, 2000) criteria for opioid dependence and be between the ages of 18-65, willing to stay on the residential research unit for up to 12 days in order to complete the full clinical trial, and on adequate birth control (if female). Exclusionary factors were clinically significant medical or psychiatric diagnoses (i.e. schizophrenia or active suicidal ideation); engaged in opioid agonist, partial agonist or antagonist treatment immediately prior to admission; pregnant or lactating; physically dependent on alcohol or sedative hypnotics; and poor oral health (i.e. active aphthous stomatitis, active oral herpes, tongue or mouth piercing, or requiring immediate dental attention). This last condition was included because the main clinical trial involved sublingual drug administration.

The Johns Hopkins Institutional Review Board approved this study and all participants provided written, informed consent. Subjects in the present analysis were primarily male (74%), Caucasian (61%) and had a mean age of 41.7 years. The primary opioid abused by subjects was either heroin (mean use 6 years, SD 9.5) or prescription opioids (mean use 4.7 years, SD 4) prior to study entry, and all subjects had been using opioids daily (96%) or near daily (at least 16 days; 4%) in the 30 days before study entry. Forty-nine subjects initially enrolled; the present report includes the 46 who completed both the placebo and naloxone challenges. Two volunteers withdrew for non-study-related personal reasons after one challenge session, and one participant withdrew after experiencing a panic attack during the naloxone challenge session. Additionally, two participants had their naloxone sessions stopped after 30 minutes for excessive withdrawal symptoms.

### 2.2 Morphine stabilization phase and description of challenge sessions

Participants were screened on an outpatient basis and then admitted to the research unit where they were stabilized on 30 mg of subcutaneously administered morphine given four times daily (120 mg/day) for 2-8 days prior to the challenge sessions (mean 4.4 days, SD 1.3). After stabilization, participants received intramuscularly administered injections of placebo and 0.4 mg naloxone in a randomized, double blind fashion in two sessions separated by at least 24 hours. Withdrawal assessments and drug effect rating scales, vital signs, and pupil measurements were collected every fifteen minutes, starting 30 minutes pre- and through 150 minutes post-injection, except for the time of drug administration (time 0). Trained research assistants, who were present during the entire session, collected the data and administered the scales.

### 2.3 Measurements

Withdrawal measurements consisted of the CINA, COWS, and VAS self-report items.

**2.3.1 CINA and COWS—**The item content and scoring of the CINA and COWS are summarized in Table 1. There is substantial overlap in content, but each scale also includes

items absent from the other. The CINA consists of 13 items — 1 purely subjective symptom item, 7 purely objective sign items, and 5 items that included subjective and objective components. The COWS consists of 11 items — 1 purely subjective symptom item, 6 objective sign items, and 4 items that included subjective and objective components. Item scoring options were specified differently for the two scales, but each scale summed the scores of its items to produce a total score. The COWS provided instructions for categorical ratings of pupil size and pulse, including an option for a zero score. On the CINA, the heart rate and blood pressure items ensured a minimum score of approximately 20 even in the absence of any withdrawal.

**2.3.2 VAS—**Visual analog scales (VAS) were single item questions that assess subjective drug effects at the time of scale completion (Preston et al., 1988). Ratings were completed on a computer; using a mouse, the subject positioned an arrow along a 100-point line marked at either end with “none” and “extremely.” VAS items in the present study were: “Do you feel any DRUG EFFECT?”, “Does the drug have any GOOD EFFECTS?”, “Does the drug have any BAD EFFECTS?”, “How HIGH are you?”, “Does this drug make you feel SICK?”, and “Do you LIKE the drug?”

**2.3.3 Pupil Diameter—**Pupil diameter was assessed with a digital pupillometer (Neuroptics, Inc.) in constant room lighting. The measurements provided by the pupillometer were also used for the pupil score in the COWS, which required observers to categorize the pupil diameter (Table 1).

### 2.4 Statistical analysis

Mean scores and standard deviations were calculated for each time point in the naloxone challenge sessions using SAS™ software, Ver. 9.1 (SAS Institute, 2003). Repeated measures regressions were used to assess significant differences on the separate opioid withdrawal measurements, using drug (naloxone versus placebo), time, and drug-by-time interaction terms. All the rest of the statistical calculations used SPSS 16.0 (SPSS Inc., Chicago, IL). Concurrent validity was assessed using Pearson correlation coefficients calculated between peak CINA, COWS, VAS items, and pupil diameter during the naloxone challenge session. Correlations of time to peak on the different measures were similarly calculated. Internal consistency reliability of the 11 COWS items was assessed with Cronbach’s alpha statistic. Lastly, inter-item correlation matrices were created to describe the association of individual COWS and CINA items to each other and to the total scale score.

## 3 Results

### 3.1 CINA vs. COWS

Overall, the COWS and CINA scales were very similar in terms of both the magnitude and time course of their withdrawal score changes in the naloxone challenge session, demonstrating the concurrent validity of the COWS. Figure 1 shows the mean scores and standard errors (SEM) of the COWS and CINA graphed versus time. The mean peak COWS (7.6) and CINA (24.4) scores occurred on average at 30 minutes post-injection, which is within the expected time range of peak withdrawal following intramuscular naloxone (Daftery, 1974;Wang et al., 1974;Judson et al., 1980). Additionally, time to peak (TTP) analysis revealed positive correlation between COWS TTP and CINA TTP ($r=0.66$, $p<0.0001$). Repeated measure regression analysis revealed statistically significant effects on COWS for drug (naloxone vs. placebo) ($F= 79.3$, $df=45$, $p<0.0001$), time ($F=15.03$, $df=495$, $p<0.0001$), and drug-by-time interaction ($F=13.82$, $df=476$, $p<0.0001$). There were also significant effects for the above three analyses on the CINA ($F=77.4$, $df=45$, $p<0.0001$), ($F=10.35$, $df=495$, $p<0.0001$), and ($F=10.94$, $df=477$, $p<0.0001$), respectively. Table 2 shows a strong positive correlation between peak COWS and CINA scores ($r=0.85$, $p<0.001$) during the naloxone challenge session.

Table 2 also shows the effect of omitting various physiological measurement items from the CINA and COWS. For the COWS, removing the pupil diameter item (COWS noPUP), heart rate item (COWS noHR), and both of these measures (COWS noPHYS) still leave these modified COWS scores highly correlated with the CINA, indicating that these items may not be needed to detect this level of opioid withdrawal with the COWS. The score on the COWS heart rate item is 0 (<80), 1 (81-100), 2(101-120), or 4 (>120). In this sample, subjects had little change in heart rate during the naloxone session (peak 7.5 bpm change from baseline); therefore, this item rarely affected the total COWS score which may explain high similarity in correlation coefficients between COWS vs. CINA and COWS without the heart rate vs. CINA. Similarly, correlations between the CINA without heart rate item (CINA noHR), systolic blood pressure score (CINA noBP), or both of these measurements (CINA noPHYS) were highly correlated with the CINA total score, as well as the COWS total score and the various modified versions of the COWS.

### 3.2 CINA and COWS vs. VAS

Two VAS items, Bad Effects and Sick, showed a similar time course but greater variability in mean score than the CINA (Figure 2). VAS mean peak scores for Bad Effects and Sick occurred on average somewhat later than the CINA peak, with the peak score occurring at 60 minutes for Bad Effects (Score=33.2) and 45 minutes for Sick (Score=28.1). The VAS time course of a rapid increase in scores after injection and then a gradual decline over 2.5 hours was very similar to the time course seen with the CINA and COWS (Figure 1). Results from repeated measures regression revealed statistically significant effects for drug condition, time, and drug-by-time interaction on these two VAS items ($p<0.0001$ in all cases). Correlation analysis showed moderately good association between peak CINA and Bad Effects ($r=0.63$, $p<0.001$) as well as Sick ($r=0.65$, $p<0.001$) (Table 2). Correlations between peak VAS and COWS were slightly lower; however, there was a strong correlation between the two VAS items ($r=0.88$, $p<0.001$). Lastly, no significant correlations were seen between peak CINA or COWS scores and VAS ratings for Good Effects, Drug Liking, or High.

### 3.3 CINA and COWS vs. Quantitative Pupil Measurements

The time course of pupil diameter change showed a mean peak increase (1.03 mm) that occurred 15 minutes after naloxone injection, followed by gradual return to baseline. Pupil diameter showed <0.27 mm change from baseline in the placebo session. Repeated measures regression using drug condition, time, and drug-by-time showed significance ($p<0.001$) in each analysis. Maximum pupil diameter and peak CINA and COWS scores showed a modest correlation ($r=0.39$, $p=0.01$ and $r=0.36$, $p=0.01$). There was no significant correlation between maximum pupil diameter and Bad Effects or Sick VAS.

### 3.4 Internal Consistency and Inter-item Correlations

Analysis of the internal consistency for the eleven COWS items revealed an overall Cronbach's alpha of 0.78, indicating good reliability. As well, there was surprisingly little inter-item correlation between individual COWS items (Table 3). Only combinations of restlessness and anxiety/irritability (0.67) as well as runny nose/tearing and yawning (0.54) were significantly correlated. A similar inter-item correlation matrix for the CINA revealed that the objective physiological measurements did not correlate well with the total CINA score, and similar items showed significant inter-item correlations as with the COWS (Table 4). Finally, the VAS items correlated with the total COWS and CINA scores about as well as did the individual items constituting the scales (Table 2).

### 3.5 Analysis of Atypical Subjects

Seven individuals did not differentiate between the effects of placebo vs. naloxone based upon VAS scores of Bad Effects. Of these individuals, four had opioid withdrawal (COWS scores ≥5) with both placebo and naloxone; two had no withdrawal in either session (COWS <5); and one person had mild withdrawal (COWS score of 6 two hours after injection) with naloxone only. There were no significant differences in demographic or history characteristics that explained those who did or did not differentiate naloxone from placebo. When these individuals were removed, no significant changes occurred in correlation, repeated measures regression, or time to peak analyses.

## 4 Discussion

The accurate and rapid assessment of opioid withdrawal is important in the clinical management of opioid dependent patients in both inpatient and outpatient settings. As well, U.S. guidelines for opioid treatment require clinical evidence of dependence in patients, which may include the presence of withdrawal (SAMHSA, 2001). Likewise, office-based outpatient treatment requires a medical professional to assess opioid withdrawal when initiating treatment with buprenorphine or buprenorphine/naloxone (Center for Substance Abuse Treatment, 2004). The present analyses provide validation of a short, easy-to-use scale for withdrawal (COWS) as well as quantification of the relationship of that scale to the CINA and single-item VAS indices of withdrawal. Our results demonstrate that the COWS correlates well with the previously validated CINA scale in the context of a standardized naloxone challenge in opioid-dependent persons. The time course of withdrawal as measured by the COWS was congruent with the pharmacologic properties of naloxone. Finally, the overlap in content of the two scales (Table 1) supports the content validity and face validity of the COWS.

Internal consistency of the COWS was high, demonstrating the scale was reliable in measuring the construct of opioid withdrawal. Inter-item correlations indicated little item overlap, providing evidence of content validity (measuring a broad range of symptoms). There was a high degree of consistency across opioid withdrawal measures in terms of identifying and tracking the syndrome over time, demonstrating concurrent validity of these measures. The time course for COWS and CINA were remarkably consistent. The similarity to CINA time course was somewhat less for the two VAS items, but the overall trend of both measures was the same. As well, the variance in the mean scores was relatively minor, except for VAS, which as single items with a larger scale range would be expected to have greater variance. This larger variance of the single-item VAS scores was probably also related to subjects' understanding of the items, personality effects on expressing discomfort, or possibly demographic and history characteristics. Nevertheless, these single-item questions may have utility in following the progress of withdrawal distress and guiding its medical management. Given the strong correlation between CINA and COWS seen in Table 3, both scales are well suited for assessing and tracking opioid withdrawal. Modifying these scales to omit objective physiological indices may not affect each scale's utility in the discrimination of the level of opioid withdrawal or guiding its medical treatment. Therefore, non-medical staff could aid in the assessment of withdrawal, and time of medical staff could be freed up for other needs. However, the physiological measures do provide objective indices to supplement the otherwise subjective responses and could thereby assist the clinician in determining false positive withdrawal responses. The choice of assessment instrument should be determined by site-specific needs, including the probability of feigned responses and the desire for objective indices.

This study has several limitations. First, relatively mild opioid withdrawal was produced, most likely due to the combination of a low naloxone dose (0.4 mg) and a modest level of morphine physical dependence (120 mg/day). However, the recognition of more severe forms of opioid withdrawal is less ambiguous for most clinicians, and the more critical need is to have scales

that are sensitive enough to distinguish mild but clinically significant withdrawal. The most useful aspect of an opioid withdrawal scale is in differentiating the presence versus absence of withdrawal, which the COWS does. The original COWS authors (Wesson and Ling, 2003) had specifically recommended that a validation be done for the low-end of the scale, which this study accomplished. Second, we did not assess external reliability of these measurements; we did not have multiple raters of the same sessions to include inter-rater reliability and did not perform multiple naloxone challenges to calculate test-retest reliability. This could be done in the future. Third, the modest correlation of COWS and CINA with pupil diameter is puzzling, given that mydriasis is a classic sign in opioid withdrawal (Himmelsbach, 1941). However, the measurement tool in this study may have affected this measure. The digital pupillometer decreased the ambient light reaching the eye by surrounding the eye before determining the pupil diameter; the intensity of lighting influences pupillary response to opioids (Weinhold and Bigelow, 1993). Fourth, this study included seven individuals who failed to distinguish placebo from naloxone. This did not change the overall results significantly but it does highlight two important points: prior literature has shown placebo can precipitate mild withdrawal in heroin-dependent individuals (Kanof et al., 1991) and not all opioid-dependent individuals respond to a naloxone challenge with signs or symptoms of withdrawal (Blachly, 1973; Wang et al., 1982). Finally, while these data document the sensitivity of these indices to opioid withdrawal, they do not address their specificity — i.e. the extent to which they may be affected by factors other than opioid withdrawal.

Even with these limitations, the validation of the COWS and correlations with the other opioid withdrawal measurement tools provide useful information for future clinical evaluation of this syndrome. The COWS and CINA followed comparable trajectories for the time course of opioid withdrawal. The VAS Bad Effects and Sick single-item assessments followed a parallel time course for withdrawal, suggesting these easily administered scales might be useful in certain settings for identifying and following opioid withdrawal. Clinicians who are not worried about feigned responses might simply use these questions to screen quickly for withdrawal and treat where appropriate. In other settings, the COWS or CINA could be used for the identification of withdrawal (with or without objective sign measurement) and for monitoring response to treatment interventions. Having easy and reliable quantification has distinct advantages when following withdrawal and setting up treatment protocols based upon these findings.

In summary, this study shows that the COWS is a valid instrument with sufficient sensitivity to detect mild opiate withdrawal. It would therefore be expected to detect moderate to severe withdrawal. The COWS, as well as the VAS items reported here, have potential uses in inpatient and outpatient treatment, in detoxification, and in research protocols. Their brevity and ease of use make them good choices for use in all these settings.

## Acknowledgments

We appreciate Linda Felch with her help analyzing the data and the many research assistants who ran the study sessions and assisted with data collection.

We would especially like to thank Lillian Salinas who helped create the figures and tables.

**Role of Funding Source:** Reckitt Benckiser Pharmaceuticals Inc. provided support and medications for use in this study. As well, this company's representatives assisted in the preparation of the protocol and review of the manuscript. NIDA also provided funding but had no other role. Grants were R01 DA08045, K24 DA023186, and T32 DA07209.

## References

American Psychiatric Association. , editor. Diagnostic and Statistical Manual of Mental Disorders. Vol. Fourth Edition. American Psychiatric Association; Washington, D.C.: 2000. Text Revision

Blachly PH. Naloxone for diagnosis in methadone programs. JAMA 1973;224:334–335. [PubMed: 4739535]

Bradley BP, Gossop M, Phillips GT, Legarda JJ. The development of an opiate withdrawal scale (OWS). Br J Addict 1987;82:1139–1142. [PubMed: 3479162]

Center for Substance Abuse Treatment. Clinical Guidelines for the use of Buprenorphine in the Treatment of Opioid Addiction. Substance Abuse and Mental Health Services Administration; Rockville, MD: 2004.

Daftery AV. Letter: Naloxone challenge in propoxyphene dependence. N Engl J Med 1974;291:979–980. [PubMed: 4414310]

Gossop M. The development of a Short Opiate Withdrawal Scale (SOWS). Addict Behav 1990;15:487–490. [PubMed: 2248123]

Haertzen CA, Meketon MJ. Opiate withdrawal as measured by the Addiction Research Center Inventory (ARCI). Dis Nerv Syst 1968;29:450–455. [PubMed: 5676126]

Haertzen CA, Meketon MJ, Hooks NT Jr. Subjective experiences produced by the withdrawal of opiates. Br J Addict Alcohol Other Drugs 1970;65:245–255. [PubMed: 5275906]

Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse 1987;13:293–308. [PubMed: 3687892]

Himmelsbach CK. The morphine abstinence syndrome, its nature and treatment. Annals of Internal Medicine 1941;15:829–39.

Isbell H. Manifestations and treatment of addiction to narcotic drugs and barbiturates. Med Clin North Am 1950;34:425–438. [PubMed: 15405124]

Judson BA, Himmelberger DU, Goldstein A. The naloxone test for opiate dependence. Clin Pharmacol Ther 1980;27:492–501. [PubMed: 7357808]

Kanof PD, Aronson MJ, Ness R, Cochrane KJ, Horvath TB, Handelsman L. Levels of opioid physical dependence in heroin addicts. Drug Alcohol Depend 1991;27:253–262. [PubMed: 1884668]

Kolb L, Himmelsbach CK. Clinical studies of drug addiction, III: a critical review of the withdrawal treatments with method of evaluating abstinence syndromes. Am J Psychiat 1938;94:759–799.

Peachey JE, Lei H. Assessment of opioid dependence with naloxone. Br J Addict 1988;83:193–201. [PubMed: 3345396]

Preston KL, Bigelow GE, Liebson IA. Butorphanol-precipitated withdrawal in opioid-dependent human volunteers. J Pharmacol Exp Ther 1988;246:441–448. [PubMed: 2457074]

SAS Institute. SAS Software. Cary, NC: 2003.

Substance Abuse and Mental Health Services Administration. 42 CFR Part 8: Opioid Drugs in Maintenance and Detoxification Treatment of Opiate Addiction; Final Rule. Federal Register 2001;66:4076–4102. [PubMed: 11503765]

Wang RI, Kochar C, Hasegawa AT, Roh BL. Initial methadone dose in treating opiate addiction. Int J Addict 1982;17:357–363. [PubMed: 7076369]

Wang RI, Wiesen RL, Lamid S, Roh BL. Rating the presence and severity of opiate dependence. Clin Pharmacol Ther 1974;16:653–658. [PubMed: 4422361]

Weinhold LL, Bigelow GE. Opioid miosis: effects of lighting intensity and monocular and binocular exposure. Drug Alcohol Depend 1993;31:177–181. [PubMed: 8436062]

Wesson, DR.; Ling, W.; Jara, G. Buprenorphine in Pharmacotherapy of Opioid Addiction: Implementation in Office-Based Medical Practice. In: Committee on Treatment of Opioid Dependence. , editor. Translating the Experience of Clinical Trials into Clinical Practice. California Society of Addiction Medicine; San Francisco, CA: 1999.

Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003;35:253–259. [PubMed: 12924748]

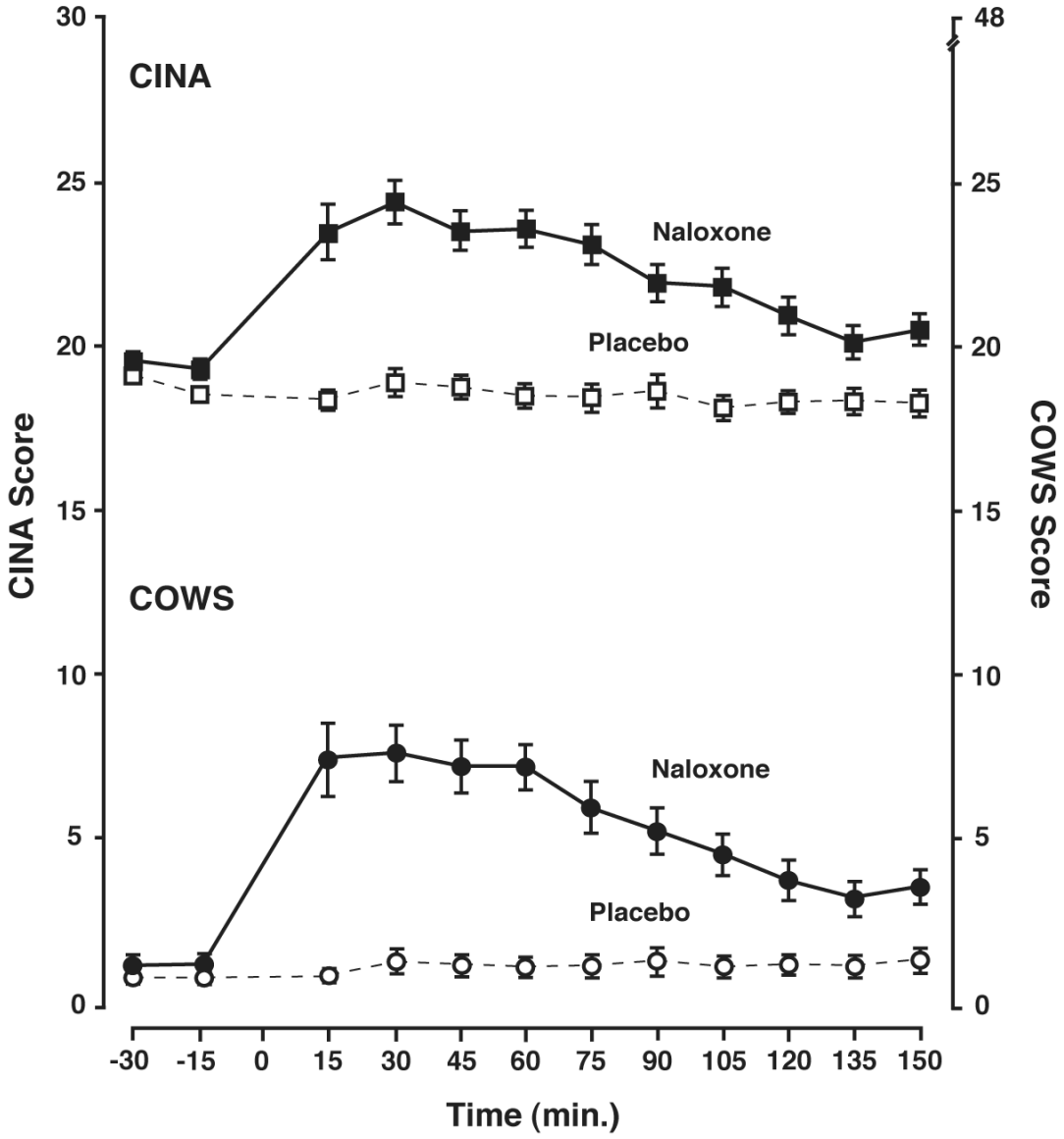



**Figure 1. Mean COWS and CINA scores (+/-SEM) vs. time**

The Clinical Opiate Withdrawal Scale (COWS) and Clinical Institute Narcotic Assessment (CINA) had peak scores in subjects on average 30 minutes post naloxone injection (+/-SEM). The two scales show a similar time course for withdrawal signs and symptoms.

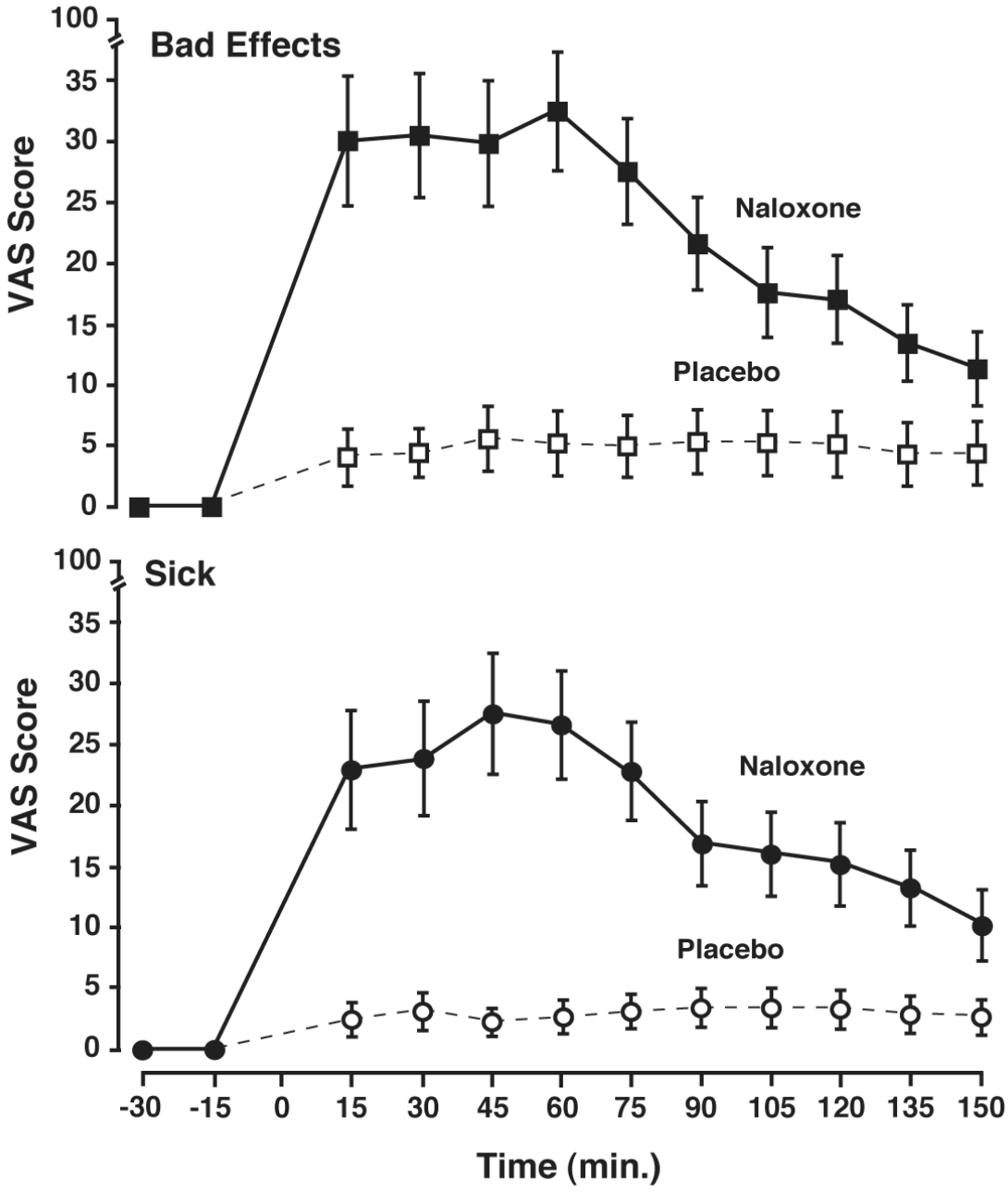



**Figure 2. Mean bad effects and sick effects VAS items (+/-SEM) vs. time**

These graphs show the average (+/-SEM) time course of subjective response on two Visual Analogue Scale (VAS) questions: (upper panel) “Does the drug have any BAD EFFECTS?” and (lower panel) “Does this drug make you feel SICK?” The over all time courses for both VAS items follow a similar course as the COWS and CINA mean scores seen in Figure 1.

## Table 1

Comparison of COWS and CINA item content and scoring.

| Sign or Symptom | Subjective vs. Objective** | Possible Scores | |
|---|---|---|---|
| | | COWS* | CINA* |
| Anxiety or irritability | S | 0,1,2,4 | ---- |
| Temperature changes | S | ---- | 0-2 |
| GI upset, including abdominal pain*** | S/O | 0-3,5 | 0,2,4,6*** |
| | | | 0-2*** |
| Restlessness | S/O | 0,1,3,5 | 0-3 |
| Bone or joint aches | S/O | 0,1,2,4 | 0-2 |
| Sweating | S/O | 0-4 | 0-3 |
| Runny nose or tearing*** | O | 0,1,2,4 | 0-2*** |
| | | | 0-2*** |
| Tremor | O | 0,1,2,4 | 0-3 |
| Gooseflesh | O | 0,3,5 | 0-3 |
| Yawning | O | 0,1,2,4 | 0-2 |
| Pupil Size | O | 0,1,2,5 | ---- |
| Pulse Rate | O | 0,1,2,4 | Pulse/10 |
| Systolic Blood Pressure (SBP) | O | ---- | SBP/10 |
| Maximum possible score | | 48 | 30 + Pulse/10 and SBP/10 |

* Entries are possible scores on each item for each instrument. If no score is shown, the scale does not include that item.

** Indicates whether item is a subjective symptom (S) or an objective sign (O). Those listed as (S/O) indicate that an item score includes assessment of both signs and symptoms, with lower scores for subjective symptom report and higher scores for objective signs.

*** The CINA contains two separate scores for these items, whereas the COWS has only one.

**Table 2**

Correlation Matrix for select opiate withdrawal assessment tools.

| | COWS | COWS noPUP | COWS noHR | COWS noPHYS | CINA | CINA noHR | CINA noBP | CINA noPHYS | Bad Effects | Sick |
|---|---|---|---|---|---|---|---|---|---|---|
| **COWS** | 1 | *** | *** | *** | *** | *** | *** | *** | *** | *** |
| **COWS noPUP** | 0.98 | 1 | *** | *** | *** | *** | *** | *** | *** | *** |
| **COWS noHR** | 1 | 0.98 | 1 | *** | *** | *** | *** | *** | *** | *** |
| **COWS noPHYS** | 0.98 | 1 | 0.98 | 1 | *** | *** | *** | *** | *** | *** |
| **CINA** | 0.85 | 0.84 | 0.84 | 0.82 | 1 | *** | *** | *** | *** | *** |
| **CINA noHR** | 0.85 | 0.85 | 0.84 | 0.84 | 0.98 | 1 | *** | *** | *** | *** |
| **CINA noBP** | 0.88 | 0.88 | 0.87 | 0.86 | 0.96 | 0.92 | 1 | *** | *** | *** |
| **CINA noPHYS** | 0.89 | 0.90 | 0.89 | 0.89 | 0.93 | 0.94 | 0.98 | 1 | *** | *** |
| **Bad Effects** | 0.57 | 0.57 | 0.56 | 0.56 | 0.63 | 0.59 | 0.64 | 0.62 | 1 | *** |
| **Sick** | 0.57 | 0.59 | 0.56 | 0.58 | 0.65 | 0.64 | 0.64 | 0.64 | 0.88 | 1 |

COWS=Clinical Opiate Withdrawal Scale. COWSnoPUP=COWS with pupil diameter categorization score removed. COWSnoHR=COWS with heart rate categorization score removed. COWSnoPHYS=COWS with both pupil diameter and heart rate scores removed. CINA=Clinical Institute Narcotic Assessment. CINAnoHR=CINA with the heart rate score removed. CINAnoBP=CINA with the systolic blood pressure score removed. CINAnoPHYS=CINA with both heart rate and blood pressure scores removed. This matrix shows a strong correlation between COWS and CINA and suggests that certain objective measurements of withdrawal, i.e. heart rate, blood pressure, and pupil size, could be omitted without losing the ability to detect opiate withdrawal. All values are significant at $p<0.001$.

**Table 3**

Inter-item correlations amongst COWS items.

| Item | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1. Pulse** | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **2. GI Upset** | 0.05* | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **3. Sweating** | 0.06* | 0.27 | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **4. Tremor** | 0.11 | 0.14 | 0.10 | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** |
| **5. Restlessness** | −0.03* | 0.33 | 0.35 | 0.13 | 1.00 | **** | **** | **** | **** | **** | **** | **** |
| **6. Yawning** | 0.09* | 0.28 | 0.34 | 0.16 | 0.40 | 1.00 | **** | **** | **** | **** | **** | **** |
| **7. Pupil Size** | 0.27 | 0.10 | 0.19 | 0.10 | 0.15 | 0.33 | 1.00 | **** | **** | **** | **** | **** |
| **8. Anxiety / Irritability** | 0.06* | 0.42 | 0.31 | 0.14 | **0.67** | 0.40 | 0.17 | 1.00 | **** | **** | **** | **** |
| **9. Bone/Joint Aches** | 0.10 | 0.22 | 0.18 | 0.11 | 0.18 | 0.08* | 0.09* | 0.33 | 1.00 | **** | **** | **** |
| **10. Gooseflesh** | 0.12 | 0.29 | 0.40 | 0.01* | 0.33 | 0.47 | 0.24 | 0.46 | 0.17 | 1.00 | **** | **** |
| **11. Runny nose / tearing** | 0.12 | 0.28 | 0.24 | 0.10 | 0.41 | **0.54** | 0.32 | 0.47 | 0.23 | 0.39 | 1.00 | **** |
| **12. Total COWS Score** | 0.24 | **0.52** | **0.55** | 0.26 | **0.66** | **0.75** | **0.53** | **0.72** | 0.35 | **0.69** | **0.69** | 1.00 |

Both the COWS and CINA inter-item correlation matrices were based on 534 observations from the 46 subjects over the entire naloxone challenge session. The overall pattern of correlations did not change appreciably when based on just the N=46 individual observations at peak opioid withdrawal.

*$p \geq 0.05$. All others $p < 0.05$. Bolded items indicate strong correlation ($r \geq 0.5$).

**Table 4**

Inter-item correlations amongst CINA items.

| Item | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1. Abdominal Changes** | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **2. Temperature Changes** | 0.27 | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **3. Nausea/Vomiting** | 0.35 | 0.33 | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **4. Muscle Aches** | 0.19 | 0.21 | 0.22 | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **5. Gooseflesh** | 0.19 | 0.49 | 0.24 | 0.16 | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** | **** |
| **6. Nasal Congestion** | 0.18 | 0.36 | 0.17 | 0.14 | 0.36 | 1.00 | **** | **** | **** | **** | **** | **** | **** | **** |
| **7. Restlessness** | 0.05* | 0.28 | 0.28 | 0.14 | 0.35 | 0.26 | 1.00 | **** | **** | **** | **** | **** | **** | **** |
| **8. Tremor** | 0.10 | 0.11 | 0.13 | 0.11 | 0.10 | −0.03* | 0.07* | 1.00 | **** | **** | **** | **** | **** | **** |
| **9. Lacrimation** | 0.14 | 0.40 | 0.25 | 0.21 | **0.50** | **0.60** | 0.36 | 0.08* | 1.00 | **** | **** | **** | **** | **** |
| **10. Sweating** | 0.19 | 0.31 | 0.24 | 0.15 | 0.29 | 0.21 | 0.20 | 0.11 | 0.22 | 1.00 | **** | **** | **** | **** |
| **11. Yawning** | 0.13 | 0.41 | 0.23 | 0.15 | 0.45 | **0.54** | 0.31 | 0.08* | **0.65** | 0.23 | 1.00 | **** | **** | **** |
| **12. HR/10** | 0.11 | 0.19 | 0.01* | 0.09 | 0.20 | 0.20 | −0.04* | 0.10 | 0.15 | 0.01* | 0.19 | 1.00 | **** | **** |
| **13. SBP/10** | 0.09 | 0.07* | −0.02* | −0.11 | 0.05* | −0.07* | 0.04* | 0.11 | 0.10 | 0.05* | 0.03* | −0.13 | 1.00 | **** |
| **14. CINA TOTAL** | 0.43 | **0.64** | **0.52** | 0.35 | **0.63** | **0.55** | 0.49 | 0.28 | **0.68** | 0.43 | **0.64** | 0.37 | 0.35 | 1.00 |

The items with highest correlation with total CINA score are temperature changes, gooseflesh, lacrimation, and yawning, as compared to restlessness, tremor, lacrimation, and nausea/vomiting in the original CINA validation study (Peachey and Lei, 1988).

*Drug Alcohol Depend*. Author manuscript; available in PMC 2010 November 1.

# REFERENCE #10

Hindawi Publishing Corporation
Journal of Addiction
Volume 2016, Article ID 7620860, 7 pages
http://dx.doi.org/10.1155/2016/7620860

*Research Article*

# Predictors of Relapse after Inpatient Opioid Detoxification during 1-Year Follow-Up

**Harsh Chalana, Tanu Kundal, Varun Gupta, and Amandeep Singh Malhari**

*Department of Psychiatry, Sri Guru Ram Dass Institute of Medical Sciences and Research, Amritsar 143501, India*

Correspondence should be addressed to Harsh Chalana; harsh_chalana@yahoo.co.in

Received 7 April 2016; Revised 31 July 2016; Accepted 24 August 2016

Academic Editor: Angela L. Stotts



*Introduction*. Relapse rate after opioid detoxification is very high. We studied the possibility that predetoxification patient characteristics might predict relapse at follow-up and thus conducted this 1-year follow-up study to assess the predictors of relapse after inpatient opioid detoxification. *Materials and Methods*. We conducted this study in our tertiary care institute in India over two-year time period (1 Jan 2014 to 31 Dec 2015). Out of 581 patients admitted, 466 patients were considered for study. *Results and Discussion*. No significant difference was found between relapsed and nonrelapsed patients regarding sociodemographic profile; however substance abuse pattern and forensic history showed significant differences. Relapsed patients abused greater amount and used injections more commonly, as compared to nonrelapsed group. Longer duration of abuse was also a significant risk factor. Patients with past attempt of opioid detoxification and family history (parental or first degree) of alcohol abuse had decreased possibility of maintaining remission during 1-year follow-up. Relapsed patients were found to abuse their spouse or parents. *Conclusion*. Our study compared profiles of relapsed and nonrelapsed patients after inpatient detoxification and concluded predictors of relapse during 1-year follow-up period. Early identification of predictors of relapse and hence high risk patients might be helpful in designing more effective and focused treatment plan.

## 1. Introduction

Relapse rate after opioid detoxification ranges from 72 to 88% after 12–36 months, despite multidisciplinary endeavors, though a six-month controlled study has shown lower relapse rate (32–70%) [1, 2]. Improvement in this rate can be done by a better understanding of pretreatment risk factors, including patient characteristics, associated with relapse after inpatient detoxification.

Early relapse after inpatient detoxification has been found to be significantly predicted by younger age, greater heroin use prior to treatment, history of injecting, and failure to enter aftercare [3]. Similarly, categories of relapse precipitant have been identified as cognition, mood, external, withdrawal, interpersonal, leaving a protected environment, drug availability, drug-related cues, craving, priming, and social pressure, in a follow-up study of 78 opiates abusers after successful opioid detoxification [4]. Abstinence has also been found to be significantly associated with completion of the 6-week inpatient treatment program and attendance at outpatient aftercare and negatively associated with a family history of substance misuse [5].

In an outpatient detoxification program, interpersonal factors, drug-related cues such as regularly meeting other drug users and being offered drugs, and persistent negative mood states have been found to be associated with relapse into opiate use [6]. Recent developments in cognitive neuroscience point to neurocognitive measures (i.e., brain-imaging measures during cognitive-task performance) as potential predictors of relapse over and above the information gained from self-report measures such as craving [7].

However, in contrast to findings in a long term study, same author earlier studied medium term follow-up outcomes after inpatient treatment of opioid dependence and concluded that patient preadmission characteristics account for a very small proportion of the variance in outcomes [3, 5]. Another 2.5-year follow-up study also found preadmission client characteristics unsuccessful in predicting achievement of abstinence [8].

We studied the possibility that predetoxification patient characteristics might predict relapse at follow-up and thus conducted this 1-year follow-up study to assess the predictors of relapse after inpatient opioid detoxification.

## 2. Materials and Methods

We conducted this study in Department of Psychiatry (Deaddiction unit), Shri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Amritsar, Punjab, India, over two-year time period (1 Jan 2014 to 31 Dec 2015), after permission from Institutional Ethics Committee. Inclusion criteria was any patient with a diagnosis of opioid dependence (as per ICD-10 criteria), admitted for detoxification in the deaddiction unit from 1 Jan 2014 to 31 Dec 2014 and consenting to participate in study. Exclusion criteria included refusal to consent, comorbid other drug addictions (except tobacco), comorbid other psychiatric or significant medical ailments, age <18 years, and known history of any adverse reaction with Naltrexone.

A total of 581 patients were admitted from 1 Jan 2014 to 31 Dec 2014 out of which 115 subjects met defined exclusion criteria or did not meet inclusion criteria. Remaining 466 patients were considered for study. A detailed history was taken and sociodemographic performa (Appendix) was completed for every patient. Average stay of subjects for detoxification varied from two to four weeks depending on withdrawal signs and symptoms. Inpatient detoxification was done as per standard protocol and medications were gradually tapered off to stop after 1–3 weeks except Quetiapine. Tab Quetiapine was used for affective symptoms as per need. After being abstinent from opioids for a minimum of 5–7 days, all patients were discharged on Tab Naltrexone 50 mg o.d. with or without Tab Quetiapine 50–200 mg/d, with regular weekly visits in outpatient unit, for next 1 year.

At least one attendant/caregiver was identified for every patient during inpatient stay, which was mostly a close family member and would stay along with patient. They were made responsible for supervising daily medication at home and were advised to make note if they suspect their patient for any substance abuse. Urine for drug abuse was done randomly to monitor relapse. A total of 2512 random samples were taken, out of which 103 were positive for opioids and they were considered as relapse. None of the patients were positive for any other substance abuse (except tobacco). Patients and their attendants were interviewed regarding relapse, which was defined as abuse of any substance, except tobacco. Alcohol abuse was also not reported by any patient or his attendant.

Adherence therapy of all patients was done at every visit by trained psychologist. Relapsed patients were compared with nonrelapsed patients with respect to their sociodemographic variables as per performa. Patients, who were lost to follow-up, were considered as relapse. Their last observations were carried forward to calculate the final data, rather than considering only the completed subjects, to avoid the bias. We tried to contact them telephonically to ask about their reason for loss to follow-up.

Relapsed and nonrelapsed groups were compared across the variables using chi-square test. A multivariate logistic regression analysis was conducted to identify variables that were independently associated with opiate abstinence. All the tests were two-tailed, and a value of $P < 0.05$ was considered statistically significant.

## 3. Results and Discussion

*3.1. Sociodemographic Profile.* A total of 466 patients were included in our study during the study period (1 Jan 2014 to 31 Dec 2014) and followed up for next 1 year (till Dec 2015). All patients were male. Sociodemographic profile has been provided in Table 1. Majority was in the age range 20–40 and had rural background. Most were married and employed with low income range. Education level was predominantly above matriculation. No significant difference was found between relapsed and nonrelapsed patients.

*3.2. Drug Use Profile.* Heroin was the most common substance of abuse in both groups as evident in Table 2. However, relapsed patients abused greater amount and used injections more commonly, as compared to nonrelapsed group. Longer duration of abuse was also a significant risk factor. Presence of craving at discharge from hospital after detoxification was significant in both groups and logistic regression showed that craving at discharge was significantly associated with relapse ($\beta = 6.86$, $P = 0.01$). Patients with past attempt of opioid detoxification and family history (parental or first degree) of alcohol abuse had decreased possibility of maintaining remission during 1-year follow-up.

*3.3. Forensic History Profile.* As shown in Table 3, patients with history of police case and incarceration were found to be significantly associated with high risk of relapse. Relapsed patients were also found to verbally and physically abuse their spouse or parents. History of self-harm was not found to be a significant risk factor for relapse.

## 4. Conclusion

(1) Our study compared profiles of relapsed and nonrelapsed patients after inpatient detoxification and concluded predictors of relapse during 1-year follow-up period. High number of young males in both groups represent pattern of drug abuse in population, in general. No female getting admitted for detoxification in our study might be due to high stigma associated with substance abuse; however females have been reported in a significant number depending on city and geographical location, in other studies [9]. Young age has been found to have high risk of relapse after inpatient detoxification [3, 10] but our study did not show any relation of age with relapse. High rural percentage in whole sample shows local area representation, as our tertiary care institute is located in rural area and mostly caters surrounding rural population. A majority of patients in both groups were married and employed, which envisages need to involve family members in treatment process. However, low economic status of patients despite high cost of substances of abuse may suggest downward economic drift of substance abusers as

Table 1: Sociodemographic profile.

| | Relapsed ($n$ = 147) | Nonrelapsed ($n$ = 319) | Chi-square value | Signific. |
|---|---|---|---|---|
| *Age* | | | | |
| Below 20 years | 45 (30.61%) | 70 (21.94%) | | |
| 20–40 years | 80 (54.42%) | 195 (61.13%) | 4.70 | Ns |
| Above 40 | 22 (14.50%) | 54 (16.93%) | | |
| *Resid. status* | | | | |
| Rural | 102 (69.39%) | 223 (69.90%) | 0.01 | Ns |
| Urban | 45 (30.61%) | 96 (30.09%) | | |
| *Marital status* | | | | |
| Single | 41 (27.89%) | 82 (25.71%) | | |
| Married | 85 (57.82%) | 190 (59.56%) | 0.25 | Ns |
| Divor./separated | 21 (14.29%) | 47 (14.73%) | | |
| *Empl. status* | | | | |
| Employed | 61 (41.50%) | 148 (46.39%) | | |
| Unemployed | 56 (38.10%) | 95 (29.78%) | 3.20 | Ns |
| Prev. employed | 30 (20.40%) | 76 (23.82%) | | |
| *Income (INR pm)* | | | | |
| 0–<10000 | 77 (52.38%) | 165 (51.72%) | | |
| 10000–<20000 | 37 (25.17%) | 91 (28.52%) | 0.78 | Ns |
| 20000–above | 33 (22.45%) | 63 (19.74%) | | |
| *Education* | | | | |
| Illiterate | 28 (19.05%) | 45 (14.11%) | | |
| Up to matric. | 39 (26.53%) | 79 (24.76%) | 3.06 | Ns |
| Above matric. | 80 (54.42%) | 195 (61.13%) | | |

well as alternate source of money being used for buying substances. Education does not appear to act as a deterrent factor for substance abuse or preventing relapse; however economic literacy awareness might be more helpful. Our findings were similar to another study done in a tertiary centre in India, to assess predictors for treatment retention in a tertiary centre in India, where all subjects were males and majority of the sample was married, educated up to matriculation, and employed and belonged to the nuclear family and urban background. Higher socioeconomic status and having a family member with substance use were associated with higher chances of treatment retention [11].

(2) Greater amount of heroin use, longer duration, history of injecting, and >3 lifetime heroin-quit attempts have been found to be significant predictors of relapse [3, 12]. Our study corroborates all these findings. We also found that heroin was the most preferred opioid of abuse among all patients, which might be due to its easy availability. Our patient base represents mainly Amritsar District, which due to its geographical location, being on border with neighboring country Pakistan, is more prone to be affected with smuggled heroin. Further, more than 1 gm of heroin, injection use, and more than 3 years of use prior to detoxification were significantly associated with relapse within 1 year. Craving was found to be present in majority of patients at time of discharge after detoxification, but it did not predict relapse in our study, though compulsive use immediately prior to hospitalization has been found to be significant in another study [13]. We noted that 2 or more previous attempts for detoxification were significantly associated with relapse; however previous studies have shown both supportive and contradictory association [14, 15]. Further, past psychiatry history or admission (except substance abuse) was not found to be associated with relapse in our findings. We also noted significant history of alcohol abuse in parents and first-degree relatives of relapsed patients, similar to another follow-up study in which 19% patients reported history of parental alcohol misuse, but surprisingly opioid abuse history in family was not found to be associated with relapse in our study [5]. Inpatient treatment and regular follow-ups have also been found to be significantly associated with abstinence [3, 5, 16]. Our studies design ensured admission and regular follow-ups for all patients which might have been a reason for lower overall relapse rate as compared to other researches.

(3) We found police case and imprisonment history to be significant in relapsed cases as shown in Table 2. One reason of high relapse in these patients could be presence of antisocial traits which itself is a risk factor for substance abuse. However, client characteristics were not found to be associated with relapse in two different studies, one a 2.5-year follow-up study and the other was a medium term follow-up study [5, 8]. One of the reasons for different results could be that, in 2.5-year follow-up study, analysis was done 2.5 years after detoxification. Another reason could be difference in culture and treatment setup. In our culture, patients without antisocial traits are better monitored by their family members while those with such traits may not be very compliant to their family values.

Table 2: Substance misuse.

| | Relapsed ($n$ = 147) | Nonrelapsed ($n$ = 319) | Chi-square | Level of sign. |
|---|---|---|---|---|
| *Substance misuse history* | | | | |
| *Principal opiate of use* | | | | |
| Morphine | 10 (6.80%) | 30 (9.40%) | | |
| Poppy husk | 12 (8.16%) | 31 (9.71%) | | |
| Heroin/smack | 70 (47.61%) | 150 (47.02%) | | |
| Tramadol | 15 (10.20%) | 20 (6.26%) | 5.15 | Ns |
| Dextropropoxyphene | 9 (6.12%) | 29 (9.09%) | | |
| Diphenoxylate | 3 (2.04%) | 9 (2.82%) | | |
| Combination of opiates | 28 (19.04%) | 50 (15.67%) | | |
| *Quantity (heroin per day)* | | | | |
| Less than 0.5 gm | 23 (17.68%) | 110 (34.48%) | | |
| 0.5–1 gm | 38 (25.85%) | 136 (42.63%) | 57.52 | 0.01 |
| More than 1 gm | 86 (58.50%) | 73 (22.88%) | | |
| *Predominant route* | | | | |
| Chase/smoke | 4 (2.72%) | 70 (21.94%) | | |
| Inject | 70 (47.61%) | 90 (28.21%) | 43.85 | 0.01 |
| Oral | 28 (19.04%) | 83 (26.01%) | | |
| Multiple | 45 (30.61%) | 76 (23.82%) | | |
| *Duration of abuse* | | | | |
| <1 year | 10 (6.80%) | 101 (31.66%) | | |
| 1–3 years | 47 (31.97%) | 118 (36.99%) | 48.85 | 0.01 |
| >3 years | 90 (61.22%) | 100 (31.34%) | | |
| *Craving at discharge* | | | | |
| Yes | 123 (83.67%) | 248 (77.74%) | 2.18 | Ns |
| No | 24 (16.32%) | 71 (22.25%) | | |
| *Number of previous attempted opiate detoxifications* | | | | |
| 0 | 45 (30.61%) | 101 (31.66%) | | |
| 1 | 13 (8.84%) | 118 (36.99%) | 49.55 | 0.01 |
| Two or more | 89 (60.54%) | 100 (31.34%) | | |
| *Past (nonaddiction) psychiatric history* | | | | |
| Yes | 36 (24.48%) | 102 (31.975) | 2.71 | Ns |
| No | 111 (75.51%) | 217 (68.02%) | | |
| *Inpatient psy treatment* | | | | |
| Yes | 9 (6.12%) | 21 (6.58%) | 0.03 | Ns |
| No | 138 (93.87%) | 298 (93.41%) | | |
| *Parental alcohol misuse* | | | | |
| Yes | 88 (59.86%) | 57 (17.86%) | 82.80 | 0.01 |
| No | 59 (40.13%) | 262 (82.13%) | | |
| *Parental opiate abuse* | | | | |
| Yes | 42 (28.57%) | 109 (6.80%) | 1.44 | Ns |
| No | 105 (71.42%) | 210 (65.83%) | | |
| *First-degree relative alcohol abuse* | | | | |
| Yes | 95 (64.62%) | 74 (23.19%) | 74.72 | 0.01 |
| No | 52 (35.37%) | 245 (76.80%) | | |
| *First-degree relative opiate abuse* | | | | |
| Yes | 55 (37.41%) | 125 (39.18%) | 0.13 | Ns |
| No | 92 (62.58%) | 194 (60.47%) | | |

Table 3: Forensic history.

| | Relapsed ($n$ = 147) | Nonrelapsed ($n$ = 319) | Chi-square | Level of sign. |
|---|---|---|---|---|
| *Forensic history* | | | | |
| *Police case registered* | | | | |
| Yes | 24 (16.32%) | 18 (5.64%) | 14.01 | 0.01 |
| No | 123 (83.67%) | 301 (94.35%) | | |
| *Imprisonment* | | | | |
| Yes | 12 (8.16%) | 7 (2.19%) | 9.17 | 0.01 |
| No | 135 (91.83%) | 312 (97.81%) | | |
| *History of verbal abuse* | | | | |
| Yes | 100 (68.02%) | 111 (34.80%) | 44.85 | 0.01 |
| No | 47 (31.97%) | 208 (65.20%) | | |
| *History of physical abuse* | | | | |
| Yes | 65 (44.22%) | 47 (14.73%) | 47.91 | 0.01 |
| No | 82 (55.78%) | 272 (85.27%) | | |
| *History of self-harm* | | | | |
| Yes | 8 (5.44%) | 20 (6.27%) | 0.12 | Ns |
| No | 139 (94.55%) | 299 (93.73%) | | |

Another reason for high relapse in the patients in our study could be habituation of offenses. Illegality is a major deterrent for opioid abuse but involvement in police cases and being in jail possibly habituates the offender, who finally does not find it as a deterrent anymore. Incarceration was found to be most common cause of dropout in a community based Indian study [9]. Involvement in legal issues has been reported as one of the major factors for treatment failure [17]. Our study also found history of verbal and physical abuse of spouse or parents as a significant risk factor for relapse. Positive family functioning and relationships have been reported to be significantly associated with improvement at follow-up [18, 19]. Problem with spouse was found to be a precipitant factor in another follow-up study [20].

To conclude, early identification of predictors of relapse and hence high risk patients might be helpful in designing more effective and focused treatment plan. More research is needed to explore patient characteristics based on our study which may help to decrease recurrent admissions and hospital expenses.

## 5. Limitations

Relapse criteria relied on interview with patients and their accompanying attendants, rather than regular urine screening tests, although random tests were done.

## Appendix

## Performa for Research Study

Name:

Sex:

MRD No.:

Serial No.:

*Socio-Demographic Profile*

Age

Below 20 years
20–40 years
Above 40

Resid. Status

Rural
Urban

Marital Status

Single
Married
Divor./Separated

Empl. Status

Employed
Unemployed
Prev. employed

Income (INR pm)

0–<10000
10000–<20000
20000–Above

Education

Illiterate
Up to Matric.
Above Matric.

*Substance Misuse*

Principal opiate of use

Morphine
Poppy Husk
Heroin/ Smack
Tramadol
Dextropropoxyphene
Diphenoxylate
Combination of opiates

Quantity (heroin per day)

Less than 0.5 gm
0.5–1 gm
More than 1 gm

Predominant route

Chase/smoke
Inject
Oral
Multiple

Duration of abuse

<1 year
1–3 years
>3 years

Craving at Discharge

Yes
No

No. of previous attempted opiate detoxification

0
1
Two or more

Past (non-addiction) Psychiatric history

Yes
No

In-patient psy treatment

Yes
No

Parental Alcohol misuse

Yes
No

Parental opiate abuse

Yes
No

First rel. alcohol abuse

Yes
No

First relative opiate abuse

Yes
No

*Forensic History*

Police Case Registered

Yes
No

Imprisonment

Yes
No

History of verbal abuse

Yes
No

History of physical abuse

Yes
No

History of Self Harm

Yes
No

## Competing Interests

The authors declare that they have no competing interests.

## References

[1] H. Chalana, J. K. Sachdeva, T. Kundal, A. S. Malhari, and R. Choudhary, "A double blind, placebo controlled, randomised study comparing Quetiapine with placebo, along with oral Naltrexone, in the treatment of opioid dependent patients," *Journal of Evolution of Medical and Dental Sciences*, vol. 4, no. 53, pp. 9158–9167, 2015.

[2] E. C. Strain, M. R. Lofwall, and J. H. Jaffe, "Opioid related disorders," in *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*, B. J. Sadock, V. A. Sadock, and P. Ruiz, Eds., p. 1382, Lippincott Williams & Wilkins, 9th edition, 2009.

[3] B. P. Smyth, J. Barry, E. Keenan, and K. Ducray, "Lapse and relapse following inpatient treatment of opiate dependence," *Irish Medical Journal*, vol. 103, no. 6, pp. 176–179, 2010.

[4] B. P. Bradley, G. Phillips, L. Green, and M. Gossop, "Circumstances surrounding the initial lapse to opiate use following detoxification," *British Journal of Psychiatry*, vol. 154, pp. 354–359, 1989.

[5] B. P. Smyth, J. Barry, A. Lane et al., "In-patient treatment of opiate dependence: medium-term follow-up outcomes," *British Journal of Psychiatry*, vol. 187, pp. 360–365, 2005.

[6] S. Unnithan, M. Gossop, and J. Strang, "Factors associated with relapse among opiate addicts in an out-patient detoxification programme," *British Journal of Psychiatry*, vol. 161, pp. 654–657, 1992.

[7] R. Marhe, M. Luijten, and I. H. A. Franken, "The clinical relevance of neurocognitive measures in addiction," *Frontiers in Psychiatry*, vol. 10, no. 4, article 185, 2014.

[8] B. J. Rounsaville, T. R. Kosten, and H. D. Kleber, "The antecedents and benefits of achieving abstinence in opioid addicts: a 2.5-year follow-up study," *The American Journal of Drug and Alcohol Abuse*, vol. 13, no. 3, pp. 213–229, 1987.

[9] Y. P. S. Balhara, R. Ranjan, A. Dhawan, and D. Yadav, "Experiences from a community based substance use treatment centre in an urban resettlement colony in India," *Journal of Addiction*, vol. 2014, Article ID 982028, 6 pages, 2014.

[10] A. Hakansson and E. Hallén, "Predictors of dropout from inpatient opioid detoxification with buprenorphine: a chart review," *Journal of Addiction*, vol. 2014, Article ID 965267, 5 pages, 2014.

[11] P. Majumder, S. Sarkar, R. Gupta, B. N. Patra, and Y. P. S. Balhara, "Predictors of retention in treatment in a tertiary care de-addiction center," *Indian Journal of Psychiatry*, vol. 58, no. 1, pp. 27–30, 2016.

[12] E. A. Woodcock, L. H. Lundahl, and M. K. Greenwald, "Predictors of buprenorphine initial outpatient maintenance and dose taper response among non-treatment-seeking heroin dependent volunteers," *Drug and Alcohol Dependence*, vol. 146, no. 1, pp. 89–96, 2015.

[13] L. Grau-López, C. Roncero, C. Daigre et al., "Risk factors for relapse in drug-dependent patients after hospital detoxification," *Adicciones*, vol. 24, no. 2, pp. 115–122, 2012.

[14] S. Darke, J. Ross, M. Teesson et al., "Factors associated with 12 months continuous heroin abstinence: findings from the Australian Treatment Outcome Study (ATOS)," *Journal of Substance Abuse Treatment*, vol. 28, no. 3, pp. 255–263, 2005.

[15] M. Gossop, L. Green, G. Phillips, and B. Bradley, "Factors predicting outcome among opiate addicts after treatment," *British Journal of Clinical Psychology*, vol. 29, no. 2, pp. 209–216, 1990.

[16] S. M. Singh, S. K. Mattoo, A. Dutt et al., "Long-term outcome of in-patients with substance use disorders: a study from North India," *Indian Journal of Psychiatry*, vol. 50, no. 4, pp. 269–273, 2008.

[17] B. Broers, F. Giner, P. Dumont, and A. Mino, "Inpatient opiate detoxification in Geneva: follow-up at 1 and 6 months," *Drug and Alcohol Dependence*, vol. 58, no. 1-2, pp. 85–92, 2000.

[18] A. S. Friedman, A. Terras, and C. Kreisher, "Family and client characteristics as predictors of outpatient treatment outcome for adolescent drug abusers," *Journal of Substance Abuse*, vol. 7, no. 3, pp. 345–356, 1995.

[19] S. S. Richter, S. A. Brown, and M. A. Mott, "The impact of social support and self-esteem on adolescent substance abuse treatment outcome," *Journal of Substance Abuse*, vol. 3, no. 4, pp. 371–385, 1991.

[20] T. R. Kosten, B. J. Rounsaville, and H. D. Kleber, "A 2.5 year follow-up of treatment retention and reentry among opioid addicts," *Journal of Substance Abuse Treatment*, vol. 3, no. 3, pp. 181–189, 1986.

# REFERENCE #11

*Ochsner Journal* 18:23–29, 2018


# Suboxone: Rationale, Science, Misconceptions

**Jennifer R. Velander, MD**

Department of Psychiatry, Ochsner Clinic Foundation, New Orleans, LA and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA

The United States is in the middle of a historically unprecedented opioid epidemic. Today, more people die of drug overdoses than any other form of accidental death, and opioid overdose rates surpass historic peak death rates from human immunodeficiency virus (HIV), gun violence, and motor vehicle accidents.[1,2] Opioid addiction rates are at all-time high. In 2014, 4.3 million people abused prescription opioids, 1.9 million people had an opioid use disorder related to prescription pain relievers, and another 586,000 people had an opioid use disorder related to heroin.[3] This epidemic is attributable to a confluence of circumstances, primarily overprescribing by physicians combined with an influx of potent heroin from Mexico. The epidemic has received additional fuel and urgency from the rise of extremely potent synthetic opioids such as fentanyl, carfentanil, and others. These synthetic drugs are often consumed unknowingly, mixed in illicit street heroin or compounded in fake versions of prescription opioids. As with other chronic medical illnesses, opioid addiction, once developed, has no cure and requires ongoing monitoring and treatment. Therapy alone and abstinence-based models rather than medication-assisted treatment have dominated opioid treatment until now. Despite detoxification combined with psychosocial treatment, relapse rates remain at 90% or higher.[4] These high relapse rates have been confirmed in populations that abuse heroin as well as prescription opioids.[5,6] Renewed use after abstinence is associated with a high overdose risk, likely the result of the loss of previous tolerance and misjudgment of safe amounts.

## HISTORIC CONTEXT

To understand the legal and medical framework for treating this epidemic, it is necessary to examine a smaller, yet not insignificant, opioid epidemic. In the late 19th and early 20th centuries, laudanum treatment for pain and opium dens associated with Chinese immigrants led to alarm and racist hysteria.[7] Physicians attempted to detoxify and safely maintain these patients with opioid medications. The Harrison Narcotics Tax Act of 1914 restricted the use of opioids to pain treatment and outlawed their use for addiction management.[8] The act framed opioid dependence and substance abuse in general as a criminal or moral rather than as a medical issue. Thirty thousand physicians, some engaged in unethical practice, some not, were prosecuted under this act.[7] Opioid addiction remained a difficult-to-treat problem, with very low recovery rates.

The work of Dole and Nyswander at Rockefeller University in the 1960s showed that the treatment of opioid addiction with methadone, a high-affinity, long-acting opioid, led to reduced criminal behavior and improved function.[9,10] The success of their research paved the way for methadone to become the first legally allowed opioid treatment for addiction since 1914. The Controlled Substances Act of 1970[11] and the Narcotic Addict Treatment Act of 1974[12] allowed dispensation of specific opioids from federally waived clinics. This legal dispensation saved lives and improved public health outcomes by helping to limit the spread of hepatitis C and HIV.[13,14] However, the utility of methadone was limited by strict regulation and the need for patients to attend special clinics—typically on a daily basis—that was undesirable for many potential patients and impossible for those who lacked access.

Buprenorphine, the opioid in Suboxone, was developed in the 1970s as a safer opioid than morphine or heroin for the treatment of pain. Studies suggested that buprenorphine could be an attractive alternative to methadone, as it could require fewer regulations because of its inherent abuse deterrence properties as a partial opioid agonist-antagonist.[15] The drug's manufacturer and the addiction treatment community lobbied for an exception to the Narcotic Addict Treatment Act to allow individual providers, rather than federally designated clinics, to prescribe buprenorphine. The Drug Addiction Treatment Act of 2000 authorized physicians via a new individual waiver to prescribe specific opioids for the treatment of opioid use disorder.[16] Buprenorphine is currently the only opioid authorized under this waiver.

## BUPRENORPHINE PHARMACOLOGY/ MECHANISM

Buprenorphine is a long-acting, high-affinity partial agonist at the mu-opioid receptor. As a long-acting agonist, buprenorphine prevents withdrawal and craving and stabilizes opioid receptors. As a high-affinity agonist, buprenorphine blocks other opioids from binding, preventing abuse of other opioids. As a partial agonist, it has a smaller effect with a ceiling, a low overdose risk, and no intoxication in the opioid dependent. Buprenorphine is available in many formulations (Table 1). The most common formulation is buprenorphine and naloxone (Suboxone) in a 4:1 ratio.[17] As an opioid antagonist with high first-pass hepatic metabolism, naloxone has no effect on sublingual use of buprenorphine but blocks intravenous or intranasal abuse of buprenorphine. In contrast, naltrexone is another opioid

**Table 1. Formulations and Indications of Buprenorphine With and Without Naloxone**

| Formulation | Route | Indication |
|---|---|---|
| **Buprenorphine + naloxone** | | |
| Suboxone | Sublingual film | Opioid use disorder |
| Zubsolv | Sublingual tablet | Opioid use disorder |
| Bunavail | Buccal film | Opioid use disorder |
| **Buprenorphine** | | |
| Subutex | Sublingual tablet | Opioid use disorder |
| Belbuca | Buccal film | Pain management |
| Buprenex | Intravenous | Pain management |
| Butrans | Transdermal patch | Pain management |
| Probuphine | 30-day subcutaneous implant | Opioid use disorder |

antagonist with greater oral bioavailability that blocks all opioids regardless of delivery method and is also US Food and Drug Administration (FDA) approved for treatment of opioid use disorder. Buprenorphine without naloxone is used for pain management and can be prescribed for opioid use disorder in sublingual film or tablet form. Except in the case of severe hepatic impairment or pregnancy, prescription of isolated buprenorphine is discouraged given the potential for intravenous abuse.

## BUPRENORPHINE DOSING

The most common dosing of buprenorphine is 8-24 mg daily. Patients need to be in sufficient opioid withdrawal for induction, typically 12-24 hours after last use. The starting dose is 4-8 mg on the first day with gradual titration. The requirement to be in withdrawal and the need for gradual titration may limit the use of buprenorphine in patients with acute pain in hospital settings. Buprenorphine is a Schedule III medication requiring special waiver (X number). Physicians can obtain waivers by taking an 8-hour course that is available online and in person.[18] Advanced practice professionals can apply for waivers as well but need a supervising physician with an X number. The initial limit is 30 patients, but this limit can be increased to 100 and then 275 patients after year-long periods. The physician must be able to offer concurrent counseling or to refer patients to counseling. In the hospital, a physician does not need to have an X number to continue buprenorphine for opioid-dependent patients with acute medical conditions as is the case with methadone.

## EVIDENCE FOR USE OF BUPRENORPHINE

As elaborated below, current evidence shows buprenorphine is superior to methadone for tolerability but equivalent for treatment retention and other outcomes. The data also indicate that buprenorphine is equal or superior to antagonist-based treatment (depot intramuscular and oral naltrexone). US Department of Veterans Affairs guidelines currently recommend either buprenorphine or methadone vs depot intramuscular naltrexone, oral naltrexone, or abstinence-based treatment.[19]

Several placebo-controlled studies document the general efficacy of buprenorphine for opioid use disorder. Patients in a Swedish treatment program randomized to buprenorphine had 1-year retention of 75% and negative urine drug tests in 75% of patients compared to 0% of patients randomized to placebo.[20] One major randomized placebo-controlled trial was terminated early because of the clear superiority of buprenorphine to placebo, with 4 times the rate of negative urine drug tests and significantly less craving in patients on buprenorphine.[21] The follow-up open-label study showed continued benefit and no increase in adverse events compared to placebo.[21] In another study of 110 patients initiated on buprenorphine, those who remained on buprenorphine after 18 months were more likely to be sober, employed, and involved in 12-step groups.[22]

Buprenorphine significantly lowers the risk of mortality and adverse outcomes. In a metaanalysis, both methadone and buprenorphine maintenance were found to be superior to detoxification alone in terms of treatment retention, adverse outcomes, and relapse rates.[6] Studies have also shown a reduction in all-cause and overdose mortality and significantly improved quality-of-life ratings with maintenance buprenorphine.[23,24] Patients on buprenorphine had reduced rates of HIV and hepatitis C transmission compared to abstinence-based therapy or detoxification alone.[13,14] Maintenance buprenorphine is also associated with better hepatitis C treatment outcomes.[25]

Suboxone has been shown to have similar efficacy to methadone when treatment conditions are similar and when patients take higher doses of Suboxone. One early study suggested that methadone was associated with better treatment retention and more negative urine drug tests than buprenorphine.[26] These findings were hypothesized to be attributable to increased dependence on the medication because of the full agonist activity and the support provided by the daily visits required for methadone treatment.[27,28] However, this study and other early studies typically underdosed buprenorphine, prescribing only 8 mg to many participants. When the subgroups on lower doses were excluded in later analyses, the outcomes between buprenorphine and methadone were the same.[26,29] This equipoise argues for buprenorphine instead of methadone, given the better safety profile of the former. As a full agonist, methadone has more than 4 times the risk of overdose than buprenorphine.[30] Buprenorphine has rarely been linked to overdoses outside of concurrent alcohol or other sedative abuse and lacks the QTc prolongation and drug-drug interactions of methadone.[31]

Oral naltrexone has been established as inferior to the extended-release depot form of naltrexone (Vivitrol) and to buprenorphine. Rates of relapse for oral naltrexone and placebo at 6 months were similar, and both were 3 times higher than the relapse rate for patients on buprenorphine maintenance.[32] Several recent studies indicate that buprenorphine and extended-release naltrexone are equally efficacious. Two naturalistic studies showed better treatment retention for buprenorphine products compared to extended-release naltrexone.[33,34] An outpatient-based randomized open-label study in Norway showed similar treatment retention and rates of negative urine drug screens between extended-release naltrexone and buprenorphine-naloxone, with significantly fewer days of heroin and illicit opioid use.[35] This study was limited in that it only followed

patients for 12 weeks. A 2017 randomized controlled study of buprenorphine and extended-release naltrexone conducted for 6 months found both medications to be equally efficacious in the per-protocol analysis.[36] However, the intention-to-treat sample showed buprenorphine to be superior to extended-release naltrexone because of the relative difficulty of induction on antagonist-based therapy, which carries a higher probability of eliciting withdrawal symptoms even weeks after the last illicit opioid use. Of the 283 patients randomized to extended-release naltrexone, 79 failed induction and ultimately relapsed.[36] Buprenorphine may also be a safer option than antagonist-based treatment. A longitudinal study showed 8 times the risk of overdose after patients left naltrexone treatment compared to agonist treatment.[37]

According to 2017 American College of Obstetricians and Gynecologists guidelines, buprenorphine is the treatment of choice for opioid-dependent women in pregnancy and is safer than methadone or medical withdrawal.[38] This recommendation for buprenorphine rather than abstinence-based or antagonist treatment is based on the high risk associated with opioid withdrawal and detoxification in pregnancy. Studies have shown higher birth weight, larger head circumference, less preterm birth, and less neonatal withdrawal symptoms in the babies of patients on buprenorphine vs methadone.[39] Of note, naltrexone is contraindicated in pregnancy, as it typically requires or precipitates opioid withdrawal. To treat opioid use disorder in pregnancy, providers historically were recommended to prescribe buprenorphine without naloxone (Subutex) given the theoretical risk of naloxone crossing the placenta.[38] However, because of the extensive first-pass hepatic metabolism of naloxone, many researchers conclude that Suboxone is as safe as or safer than Subutex in pregnancy, except in cases of severe hepatic impairment. Recent studies show little placental transfer of naloxone and equivalent safety between buprenorphine/naloxone and buprenorphine alone.[40-43]

In line with the move toward maintenance and chronic opioid treatment rather than detoxification and abstinence, studies suggest that treatment duration should be years rather than weeks to months for most patients. The FDA recently adjusted its labeling to state that some patients will benefit from indefinite buprenorphine treatment.[44] Tapers should be individualized because of the potential for worsened outcomes with forced tapers. The risk of relapse is equally high after 2-week and 12-week stabilization periods before taper, with no further benefit from counseling posttaper.[4] Young adults randomized to 12 weeks of maintenance buprenorphine before taper had fewer positive urine drug tests, adverse outcomes, and dropouts than those randomized to detoxification alone. No significant difference in relapse rates persisted at follow-up, suggesting that the benefit to maintenance, at least for the short term, only lasts as long as the maintenance treatment.[45]

Waiver guidelines dictate that physicians have the ability to refer patients to adjunctive psychosocial therapy. The benefit of psychosocial treatment in addition to buprenorphine maintenance, however, is uncertain, with only 4 of 8 studies showing benefit.[46] Certain subgroups, such as heroin users or those with severe disease, may benefit more.[47] Therapy-based outcomes are difficult to measure, particularly in this population because of the chronic nature of addiction, and therapy and support needs may wax and wane over time. Further, studies often exclude patients with other substance use disorders, selecting more stable patients than typically present in the general population. In my experience as an addiction psychiatrist, patients commonly need more support in the initial stages of treatment, such as that provided in intensive outpatient programs, to maintain engagement and address risk factors.

## SYSTEM-BASED TREATMENT WITH BUPRENORPHINE

The multiple models for buprenorphine treatment range from minimal support to extensive scaffolded systems. Most commonly, buprenorphine is prescribed by solo practitioners (41.6% psychiatrists, 36.7% primary care physicians) in private practice or small clinic settings who leave the responsibility for psychotherapy largely up to the patient.[48] This practice allows for greater access but also runs the risk of inadequate treatment and diversion. Several system-based approaches have been developed with numerous levels of expertise, providers, and support (Table 2).[49-54] The benefits of system-based approaches include expanded and rapid access to treatment, more support for prescribers, and the ability to adjust levels of care based on the patient's stability. Ideally, a healthcare system would incorporate elements of several models with routes to treatment initiation in emergency rooms, inpatient medical floors, and primary care and psychiatry offices, in addition to higher levels of psychiatric and addiction care in inpatient and intensive outpatient substance abuse programs.

## MISCONCEPTIONS ABOUT BUPRENORPHINE

Despite substantial evidence for its efficacy and well-developed models of care, buprenorphine remains underutilized. The need for further prescribers is particularly evident in the rural United States and the South.[55] As of 2015, the majority of US counties (53.4%), most of them rural, were without a buprenorphine prescriber.[48] Louisiana has only 209 providers statewide, with the vast majority concentrated in the New Orleans area.[56] Most waivered physicians treat far fewer patients than the 275 potential maximum. Studies suggest that lack of experience and education in the use of buprenorphine is a major reason for its underutilization.[57] As an addiction psychiatrist, I have encountered several misconceptions among colleagues and patients who are unfamiliar with buprenorphine that have led to resistance to utilizing it. I discuss 5 of these misconceptions below.

*Misconception 1: Suboxone just substitutes one drug for another*. If used as directed, buprenorphine-naloxone is a medication, not a substance. It is a stable, safe, long-acting medication with a ceiling effect. It is prescribed for the specific effect of improving patients' physical and mental health and preventing HIV, hepatitis C, other infectious diseases, and death. Thus, it has a clear indication, unlike substances of abuse. Suboxone would likely be more widely accepted as a medication if analogous treatments were available for other addictions. However, no partial-agonist treatment or similarly effective medication is available for alcohol or cocaine use disorders.[58]

**Table 2. System-Based Models of Buprenorphine Maintenance Treatment**

| Model | Description | Evidence |
|---|---|---|
| Vermont Hub and Spoke[49] | The state of Vermont was divided into 5 administrative sections, each with a hub clinic, led by an addiction psychiatrist who initiates treatment and then refers to a local hub of waivered primary care practitioners who can refer patients back to the hub if they destabilize. | Of 7,212 people identified in the state with a diagnosis of opioid use disorder, 5,298 were receiving opioid agonist treatment. Sixty-four percent more physicians were waivered to prescribe buprenorphine, and waivered physicians provided treatment to 50% more patients. |
| Massachusetts Nursing Care Model[50] | In this statewide system, specially trained nurse care managers support prescribing physicians, providing clinical and administrative care with psychiatric resources available onsite or nearby. | The number of waivered physicians increased by 375%. |
| Project Echo[51] | Via this telemedicine system in New Mexico, specialists provide video-based education and mentoring to primary care physicians in rural communities. | In terms of having the most buprenorphine-waivered physicians per capita, New Mexico's state ranking progressed from fourteenth to fourth. |
| Inpatient-Initiated, Medication-Assisted Treatment[52,53] | Hospitalists induce patients on buprenorphine during admissions for other medical issues and refer them to affiliated addiction clinics. | Patients randomized to maintenance buprenorphine treatment during hospitalization were much more likely to follow through with outpatient treatment than those randomized to detoxification (72.2% vs 11.9%). |
| | | Of 40 patients induced on buprenorphine, 49% linked to a clinic, with 39% remaining in treatment after 30 days, 27% after 90 days, and 18% after 180 days. |
| Emergency Department (ED)–Initiated, Medication-Assisted Treatment[54] | In the ED, take-home doses of buprenorphine are dispensed to bridge patients to appointments with outpatient substance abuse clinics within 3 days. | Compared to screening and referral alone, initiation of buprenorphine maintenance in the ED led to higher treatment engagement rates (78% vs 45%). |

*Misconception 2: Suboxone is a "failure of willpower" or "giving up."* Addiction is a medical disease, not a moral failure. Treatment with a partial agonist allows stabilization of opioid receptors so that patients are able to make changes in lifestyle, behaviors, and psychiatric condition to allow ultimate recovery rather than cycles of relapses. The mortality associated with any relapse on opioids is too high and too final.

*Misconception 3: Suboxone is incompatible with 12-step groups like Alcoholics Anonymous and Narcotics Anonymous*. The 12-step groups distinguish between taking medications as prescribed and substance use. Alcoholics Anonymous and Narcotics Anonymous were previously hostile to antidepressants and disulfiram (Antabuse), stating that patients on those medications were not really sober, but the organizations have changed their stance. Numerous substance abuse treatment programs combine Suboxone use with 12-step facilitation. The Hazelden Betty Ford Foundation, possibly the most respected substance abuse treatment institution, has been pioneering integration of partial-agonist therapy with 12-step groups.[59] However, real stigma to partial-agonist therapy exists and exerts undue pressure on 12-step participants to prematurely discontinue a lifesaving medication.[60]

*Misconception 4: Patients can get "high" or "loaded" on Suboxone*. Intoxication from Suboxone does not occur if a patient is opioid dependent. Intoxication occurs only in patients who combine Suboxone with other substances, do not take it as directed, or use it to medicate withdrawal between episodes of full-agonist opioid abuse. This misuse can be addressed with increased monitoring, urine drug testing, and film/pill counts. Patients are safe to drive while on maintenance doses, and cognitive function in patients on buprenorphine maintenance is likely improved compared to other opioid users.[31]

*Misconception 5: Patients will just sell Suboxone*. Physicians can monitor for diversion of Suboxone by instituting film/pill checks and checking urine buprenorphine levels. Furthermore, diversion of medications is not unique to opioids or buprenorphine. The rates of diversion are similar between buprenorphine and antibiotics, both approximately 20%.[61] Also the vast majority of diverted buprenorphine is used to self-treat addiction; 64% of opioid users in one

study reported using illicit buprenorphine because they were unable to afford or to access treatment.[62]

## CONCLUSION

Buprenorphine-naloxone remains an underutilized treatment for opioid use disorder despite its efficacy, safety, and relative ease of use. To fully address the vast opioid epidemic, more physicians other than addiction subspecialists should be enlisted to diagnose and treat opioid use disorder. With familiarization, training, and formation of support networks, buprenorphine could become a vital part of the community practice and health system response to the opioid epidemic.

## ACKNOWLEDGMENTS

*The author has no financial or proprietary interest in the subject matter of this article*.

## REFERENCES

1. Centers for Disease Control and Prevention; National Center for Health Statistics. Accidents or unintentional injuries. http://www.cdc.gov/nchs/fastats/accidental-injury.htm. Updated March 17, 2017. Accessed December 19, 2017.
2. Katz J. Drug deaths in America are rising faster than ever. *The New York Times*. http://www.nytimes.com/interactive/2017/06/05/upshot/opioid-epidemic-drug-overdose-deaths-are-rising-faster-than-ever.html. Published June 5, 2017. Accessed October 30, 2017.
3. Center for Behavioral Health Statistics and Quality; Substance Abuse and Mental Health Services Administration. *Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf. Published September 2015. Accessed January 19, 2018.
4. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011 Dec;68(12):1238-1246. doi: 10.1001/archgenpsychiatry.2011.121.
5. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD002209. doi: 10.1002/14651858.CD002209.pub2.
6. Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane Database Syst Rev*. 2016 May 9;(5):CD011117. doi: 10.1002/14651858.CD011117.pub2.
7. Hamid A. *Drugs in America: Sociology, Economics, and Politics*. Gaithersburg, MD: Aspen Publishers, Inc.; 1998:86.
8. Schaffer Library of Drug Policy. The Harrison Narcotic Act (1914). http://www.druglibrary.org/schaffer/library/studies/cu/cu8.html. Accessed January 19, 2018.
9. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *JAMA*. 1965 Aug 23;193:646-650.
10. Dole VP. Methadone maintenance treatment for 25,000 heroin addicts. *JAMA*. 1971 Feb 15;215(7):1131-1134.
11. Pub L No. 91-513, 84 Stat 1236. https://www.gpo.gov/fdsys/pkg/STATUTE-84/pdf/STATUTE-84-Pg1236.pdf. Accessed January 19, 2018.
12. Pub L No. 93-281, 88 Stat 124. http://www.naabt.org/documents/Narcotic-Addict-Act-1974-public-law-93-281.pdf. Accessed January 19, 2018.
13. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev*. 2011 Aug 10;(8):CD004145. doi: 10.1002/14651858.CD004145.pub4.
14. Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. *JAMA Intern Med*. 2014 Dec;174(12):1974-1981. doi: 10.1001/jamainternmed.2014.5416.
15. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry*. 1978 Apr;35(4):501-516.
16. Pub L No. 106-301, 114 Stat 1104. https://www.gpo.gov/fdsys/pkg/PLAW-106publ310/pdf/PLAW-106publ310.pdf. Accessed January 19, 2018.
17. Mendelson J, Jones RT. Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: why the 4:1 ratio for treatment? *Drug Alcohol Depend*. 2003 May 21;70(2 Suppl):S29-S37.
18. Substance Abuse and Mental Health Services Administration. Buprenorphine training for physicians. http://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training. Updated July 7, 2016. Accessed December 19, 2017.
19. US Department of Veterans Affairs; The Management of Substance Use Disorders Work Group. VA/DoD clinical practice guideline for the management of substance use disorders. http://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf. Published December 2015. Accessed October 10, 2017.
20. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet*. 2003 Feb 22;361(9358):662-668.
21. Fudala PJ, Bridge TP, Herbert S, et al; Buprenorphine/Naloxone Collaborative Study Group. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003 Sep 4;349(10):949-958.
22. Parran TV, Adelman CA, Merkin B, et al. Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. *Drug Alcohol Depend*. 2010 Jan 1;106(1):56-60. doi: 10.1016/j.drugalcdep.2009.07.013.
23. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017 Apr 26;357:j1550. doi: 10.1136/bmj.j1550.
24. Mitchell SG, Gryczynski J, Schwartz RP, et al. Changes in quality of life following buprenorphine treatment: relationship with treatment retention and illicit opioid use. *J Psychoactive Drugs*. 2015 Apr-Jun;47(2):149-157. doi: 10.1080/02791072.2015.1014948.
25. Norton BL, Beitin A, Glenn M, DeLuca J, Litwin AH, Cunningham CO. Retention in buprenorphine treatment is associated with improved HCV care outcomes. *J Subst Abuse Treat*. 2017 Apr;75:38-42. doi: 10.1016/j.jsat.2017.01.015.
26. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008 Apr 16;(2):CD002207. doi: 10.1002/14651858.CD002207.pub3.
27. Hser YI, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*. 2014 Jan;109(1):79-87. doi: 10.1111/add.12333.

28. Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction*. 2016 Apr;111(4):695-705. doi: 10.1111/add.13238.
29. Thomas CP, Fullerton CA, Kim M, et al. Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv*. 2014 Feb 1;65(2):158-170. doi: 10.1176/appi.ps.201300256.
30. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend*. 2009 Sep 1;104(1-2):73-77. doi: 10.1016/j.drugalcdep.2009.03.020.
31. Soyka M. New developments in the management of opioid dependence: focus on sublingual buprenorphine-naloxone. *Subst Abuse Rehabil*. 2015 Jan 6;6:1-14. doi: 10.2147/SAR.S45585.
32. Schottenfeld RS, Chawarski MC, Mazlan M. Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008 Jun 28;371(9631):2192-2200. doi: 10.1016/S0140-6736(08)60954-X.
33. Morgan JR, Schackman BR, Leff JA, Linas BP, Walley AY. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. *J Subst Abuse Treat*. 2018 Feb;85:90-96. doi: 10.1016/j.jsat.2017.07.001.
34. Crits-Christoph P, Markell HM, Gibbons MB, et al. A naturalistic evaluation of extended-release naltrexone in clinical practice in Missouri. *J Subst Abuse Treat*. 2016 Nov;70:50-57. doi: 10.1016/j.jsat.2016.07.014.
35. Tanum L, Solli KK, Latif ZE, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry*. 2017 Dec 1;74(12):1197-1205. doi: 10.1001/jamapsychiatry.2017.3206.
36. Lee JD, Nunes EV, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet*. 2017 Nov 14. doi: 10.1016/S0140-6736(17)32812-X. [Epub ahead of print].
37. Digiusto E, Shakeshaft A, Ritter A, O'Brien S, Mattick RP; NEPOD Research Group. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction*. 2004 Apr;99(4):450-460.
38. The American College of Obstetricians and Gynecologists. ACOG Committee Opinion, Number 711. Opioid use and opioid use disorder in pregnancy. https://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Opioid-Use-and-Opioid-Use-Disorder-in-Pregnancy. Published August 2017. Accessed October 10, 2017.
39. Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction*. 2016 Dec;111(12):2115-2128. doi: 10.1111/add.13462.
40. Wiegand SL, Swortwood MJ, Huestis MA, Thorp J, Jones HE, Vora NL. Naloxone and metabolites quantification in cord blood of prenatally exposed newborns and correlations with maternal concentrations. *AJP Rep*. 2016 Oct;6(4):e385-e390.
41. Debelak K, Morrone WR, O'Grady KE, Jones HE. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy-initial patient care and outcome data. *Am J Addict*. 2013 May-Jun;22(3):252-254. doi: 10.1111/j.1521-0391.2012.12005.x.
42. Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. *Obstet Gynecol*. 2015 Feb;125(2):363-368. doi: 10.1097/AOG.0000000000000640.
43. Jumah NA, Edwards C, Balfour-Boehm J, et al. Observational study of the safety of buprenorphine+naloxone in pregnancy in a rural and remote population. *BMJ Open*. 2016 Oct 31;6(10):e011774. doi: 10.1136/bmjopen-2016-011774.
44. US Food and Drug Administration. FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. http://www.fda.gov/Drugs/DrugSafety/ucm575307.htm. Published September 20, 2017. Updated September 26, 2017. Accessed December 19, 2017.
45. Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008 Nov 5;300(17):2003-2011. doi: 10.1001/jama.2008.574.
46. Carroll KM, Weiss RD. The role of behavioral interventions in buprenorphine maintenance treatment: a review. *Am J Psychiatry*. 2017 Aug 1;174(8):738-747. doi: 10.1176/appi.ajp.2016.16070792.
47. Weiss RD, Griffin ML, Potter JS, et al. Who benefits from additional drug counseling among prescription opioid-dependent patients receiving buprenorphine-naloxone and standard medical management? *Drug Alcohol Depend*. 2014 Jul 1;140:118-122. doi: 10.1016/j.drugalcdep.2014.04.005.
48. Rosenblatt RA, Andrilla CH, Catlin M, Larson EH. Geographic and specialty distribution of US physicians trained to treat opioid use disorder. *Ann Fam Med*. 2015 Jan-Feb;13(1):23-26. doi: 10.1370/afm.1735.
49. Brooklyn JR, Sigmon SC. Vermont hub-and-spoke model of care for opioid use disorder: development, implementation, and impact. *J Addict Med*. 2017 Jul/Aug;11(4):286-292. doi: 10.1097/ADM.0000000000000310.
50. LaBelle CT, Han SC, Bergeron A, Samet JH. Office-based opioid treatment with buprenorphine (OBOT-B): statewide implementation of the Massachusetts collaborative care model in community health centers. *J Subst Abuse Treat*. 2016 Jan;60:6-13. doi: 10.1016/j.jsat.2015.06.010.
51. Komaromy M, Duhigg D, Metcalf A, et al. Project ECHO (extension for community healthcare outcomes): a new model for educating primary care providers about treatment of substance use disorders. *Subst Abus*. 2016;37(1):20-24. doi: 10.1080/08897077.2015.1129388.
52. Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Intern Med*. 2014 Aug;174(8):1369-1376. doi: 10.1001/jamainternmed.2014.2556.
53. Trowbridge P, Weinstein ZM, Kerensky T, et al. Addiction consultation services - linking hospitalized patients to outpatient addiction treatment. *J Subst Abuse Treat*. 2017 Aug;79:1-5. doi: 10.1016/j.jsat.2017.05.007.
54. D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA*. 2015 Apr 28;313(16):1636-1644. doi: 10.1001/jama.2015.3474.
55. Jones EB. Medication-assisted opioid treatment prescribers in federally qualified health centers: capacity lags in rural areas. *J Rural Health*. 2018 Dec;34(1):14-22. doi: 10.1111/jrh.12260.
56. Louisiana Commission on Preventing Opioid Abuse. The Opioid Epidemic: Evidence-Based Strategies Legislative Report, April 2017. http://www.pharmacy.la.gov/assets/docs/Public_Library/LCPOA_FinalReportPublic_2017-0331.pdf. Published March 31, 2017. Accessed October 10, 2017.

57. Netherland J, Botsko M, Egan JE, et al; BHIVES Collaborative. Factors affecting willingness to provide buprenorphine treatment. *J Subst Abuse Treat*. 2009 Apr;36(3):244-251. doi: 10.1016/j.jsat.2008.06.006.
58. Substance Abuse and Mental Health Services Administration. Treatments for substance use disorders. https://www.samhsa.gov/treatment/substance-use-disorders. Updated August 9, 2016. Accessed December 19, 2017.
59. Hazelden Betty Ford Foundation. COR-12™ opioid treatment program: making a difference in Oregon. http://www.hazeldenbettyford.org/articles/2016-news/cor-12-opioid-treatment-making-a-difference. Published December 1, 2016. Accessed December 19, 2017.
60. Monico LB, Gryczynski J, Mitchell SG, Schwartz RP, O'Grady KE, Jaffe JH. Buprenorphine treatment and 12-step meeting attendance: conflicts, compatibilities, and patient outcomes. *J Subst Abuse Treat*. 2015 Oct;57:89-95. doi: 10.1016/j.jsat.2015.05.005.
61. Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. *J Addict Med*. 2014 Sep-Oct;8(5):315-326. doi: 10.1097/ADM.0000000000000045.
62. Bazazi AR, Yokell M, Fu JJ, Rich JD, Zaller ND. Illicit use of buprenorphine/naloxone among injecting and noninjecting opioid users. *J Addict Med*. 2011 Sep;5(3):175-180. doi: 10.1097/ADM.0b013e3182034e31.

# REFERENCE #12

Neurotherapeutics (2015) 12:825–836
DOI 10.1007/s13311-015-0387-1

REVIEW

# Cannabidiol as a Potential Treatment for Anxiety Disorders

**Esther M. Blessing**[1] · **Maria M. Steenkamp**[1] · **Jorge Manzanares**[1,2] · **Charles R. Marmar**[1]

Published online: 4 September 2015


**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 $\Delta^{9}$-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, anticonvulsant, 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 ($CB_1R$), 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: $CB_1R$, 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 $CB_1R$, endogenous $CB_1R$ ligands, or "endocannabinoids" (eCBs) were discovered, namely anandamide (AEA) and 2-arachidonoylglycerol (reviewed in [22]). The $CB_1R$ is an inhibitory $G_{i/o}$ protein-coupled receptor that is mainly localized to nerve terminals, and is expressed on both γ-aminobutryic acid-ergic and glutamatergic neurons. eCBs are fatty acid derivatives that are synthesized on demand in response to neuronal depolarization and $Ca^{2+}$ 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 $CB_1Rs$, 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 $CB_1R$ and related $CB_2$ 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 $CB_1R$ 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 capsacin (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 $CB_1Rs$ 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 $CB_1R$ activation is complex: $CB_1R$ activation may enhance or reduce fear expression, depending on brain locus and the eCB ligand [34]; however, $CB_1R$ activation potently enhances fear extinction [35], and can prevent fear reconsolidation. Genetic manipulations that impede

$CB_1R$ 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–$CB_1R$ signaling in the amygdala mediates the anxiogenic effects of corticotropin-releasing hormone [37], and $CB_1R$ 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 $CB_1R$ availability and reduced peripheral AEA, suggestive of reduced eCB tone [42].

Accordingly, $CB_1R$ activation has been suggested as a target for anxiolytic drug development [15, 43, 44]. Proposed agents for enhancing $CB_1R$ activation include THC, which is a potent and direct agonist; synthetic $CB_1R$ 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 $CB_1R$, it functions as an indirect agonist, potentially via augmentation of $CB_1R$ 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 $CB_1R$-activating agents to serve as anxiolytic drugs. First, $CB_1R$ 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 $CB_1R$ 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 $CB_1R$ 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 $CB_1Rs$ [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 |
| Resstel et al. [63] | WR | i.p. | **10**mg/kg, acute | CFC | Anxiolytic | NA |
| Campos et al. [64] | WR | dlPAG | 15.0, **30.0**, 60.0 nmol/0.2 μl, acute | EPM<br>VCT | Anxiolytic<br>Anxiolytic | Both effects ↓ by intra-dlPAG WAY100635 but not intra-dlPAG AM251 |
| Bitencourt et al. [65] | WR | i.c.v. | **2.0** μg/μl<br>5 min before extinction, acute | CFC extinction<br>EPM before and 24 h after CFC | Anxiolytic<br>No effect before CFC<br>Anxiolytic following CFC | Extinction effect ↓ by SR141716A but not capsazepine |
| Campos et al. [66] | WR | dlPAG | **30**, 60 mg/kg, acute | EPM | Anxiolytic | Intra-dlPAG capsazepine renders 60 mg/kg anxiolytic |
| Resstel et al. [67] | WR | i.p. | 1, **10** or 20 mg/kg, acute | RS<br>EPM 24 h following RS | Anxiolytic,<br>↓ Pressor<br>↓ Tachycardia<br>Anxiolytic | All effects ↓ by systemic WAY100635 |
| Soares et al. [68] | WR | dlPAG | 15, **30** or **60**nmol, acute | ETM<br>PAG E-stim | Anxiolytic<br>Panicolytic<br>Panicolytic | All effects ↓ by intra-dlPAG WAY100635 but not AM251 |
| Long et al. [69] | C57BL/6 J mice | i.p. | **1**, 5, 10, **50**mg/kg, chronic, daily/21 d | EPM<br>L-DT<br>SI<br>OF | No effect<br>1 mg/kg anxiolytic<br>No effect<br>50 mg/kg anxiolytic | NA |
| Lemos et al. [70] | WR | i.p.<br>PL<br>IL | **10**mg/kg IP, **30**nmol intra-PL and intra-IL, acute | CFC | IP and PL anxiolytic IL anxiogenic | 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<br>VCT | Anxiolytic<br>Anxiolytic | Both effects ↓ by intra BNST WAY100635 |
| Granjeiro et a l. [73] | WR | Intracisternal | 15, **30**, and 60 nmol, acute | RS<br>EPM 24 h after RS | Anxiolytic, ↓Pressor ↓Tachycardia<br>Anxiolytic | NA |
| Deiana et al. [74] | SM | i.p.<br>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<br>EPM<br>OF | ↓ REM sleep suppression<br>Anxiolytic<br>Anxiolytic | NA |
| Gomes et al. [79] | WR | BNST | **15**, **30**, **60** nmol, acute | CFC | Anxiolytic | Both effects ↓ by intra-BNST WAY100635 |
| El Batsh et al. [80] | LE-H R | 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<br>NSF | Anxiolytic<br>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<br>Panicolytic | Panicolytic effect ↓ by intra-dlPAG 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<br>↑ Tachydardia | Effect ↓ by WAY100635 |
| Twardowschy et al. [86] | SM | i.p. | **3** mg/kg, acute | PS | Panicolytic | Effects ↓ by IP WAY100635 |
| Focaga et al. [87] | WR | PL | 15, **30**, 60 nmol, acute | EPM<br>EPM after RS<br>CFC | Anxiogenic<br>Anxiolytic<br>Anxiolytic | All effects ↓ by intra PL WAY100635<br>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 dlSC | Panicolytic | Both effects ↓ by AM251 |

Effective doses are in bold

Receptor specific agents: AM251 = cannabinoid receptor type 1 ($CB_1R$) inverse agonist; WAY100635 = 5-hydroxytryptamine 1A antagonist; SR141716A = $CB_1R$ antagonist; rimonabant = $CB_1R$ 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

Anticomplusive effects: MBT = reduced burying

Panicolytic effects: ETM = decreased escape; $GABA_A$ blockade in dlSC = 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; dlPAG = 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 dlPAG; 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; dlSC = 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 $CB_1$R 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 $CB_1$R 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 $CB_1$Rs, 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 $CB_1$Rs 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 $CB_1$R activation, without involvement of TRPV1 receptors [65]. Further studies showed $CB_1$Rs 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 $CB_1R$ 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 anticompulsive 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 $CB_1R$ activation may play a limited role. By contrast, $CB_1R$ activation appears to mediate CBD's anticompulsive 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 $CB_1R$ 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 $CB_1R$ 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<br>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<br>↓ VAMS scores<br>↓ 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<br>SPECT | ↓ VAMS scores |
| Bhattacharyya et al. [103] | 15 HV DBP | Oral 600 mg, acute, 1, 2, 3 h | STAI scores<br>VAMS scores | ↓ STAI scores<br>↓ VAMS scores |
| Crippa et al. [104] | SAD and HC DBP | Oral 400 mg, acute, 75 and 140 min | VAMS before SPECT<br>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 = $^{\Delta}$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<br>↑ 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.<br>↑ 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-photo 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 $CB_1$Rs 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.

## References

1. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med 2007;146:317-325.
2. Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. J Affect Disord 2002;68:183-190.
3. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: a meta-analytic review. Clin Psychol Rev 2007;27:572-581.
4. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593-602.
5. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:629-640.
6. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21:718-779.
7. Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. Am J Psychiary 2001;158:1989-1992.
8. Ballenger JC. Remission rates in patients with anxiety disorders treated with paroxetine. J Clin Psychiatry 2004;65:1696-1707.
9. Krystal JH, Rosenheck RA, Cramer JA, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA 2011;306:493-502.
10. Shin HJ, Greenbaum MA, Jain S, Rosen CS. Associations of psychotherapy dose and SSRI or SNRI refills with mental health outcomes among veterans with PTSD. Psychiatr Serv 2014;65:1244-1248.
11. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci 2009;30:515-527.

12. Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FS. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Philos Trans R Soc Lond Ser B Biol Sci 2012;367:3364-3378.
13. Schier ARD, Ribeiro NP, Silva AC, et al. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. Rev Bras Psiquiatr 2012;34:S104-S117.
14. Schier ARD, de Oliveira Ribeiro NP, Coutinho DS, et al. Antidepressant-like and anxiolytic-like effects of cannabidiol: A chemical compound of *Cannabis sativa*. CNS Neurol Disord Drug Targets 2014;13:953-960.
15. Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. Endocannabinoid system and mood disorders: priming a target for new therapies. Pharmacol Ther 2013;138:18-37.
16. Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol—recent advances. Chem Biodivers 2007;4:1678-1692.
17. Marco EM, Garcia-Gutierrez MS, Bermudez-Silva FJ, et al. Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects. Front Behav Neurosci 2011;5:63.
18. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55:791-802.
19. Robson PJ, Guy GW, Di Marzo V. Cannabinoids and schizophrenia: therapeutic prospects. Curr Pharm Design 2014;20:2194-2204.
20. Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a *Cannabis sativa* constituent. Curr Drug Saf 2011;6: 237-249.
21. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Delta(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol 2015;172:737-753.
22. Di Marzo V, Bisogno T, De Petrocellis L. Anandamide: Some like it hot. Trends Pharmacol Sci 2001;22:346-349.
23. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science 2002;296: 678-682.
24. Battista N, Di Tommaso M, Bari M, Maccarrone M. The endocannabinoid system: An overview. Front Behav Neurosci 2012;6:9.
25. Lee SH, et al. Multiple forms of endocannabinoid and endovanilloid signaling regulate the tonic control of GABA release. J Neurosci 2015;35:10039-10057.
26. Kauer JA, Gibson HE. Hot flash: TRPV channels in the brain. Trends Neurosci 2009;32:215-224.
27. Aguiar DC, Moreira FA, Terzian AL, et al. Modulation of defensive behavior by transient receptor potential vanilloid type-1 (TRPV1) channels. Neurosci Biobehav Rev 2014;46:418-428.
28. Silvestri C, Di Marzo V. The endocannabinoid system in energy homeostasis and the etiopathology of metabolic disorders. Cell Metab 2013;17:475-490.
29. Castillo PE, Younts TJ, Chavez AE, Hashimotodani Y. Endocannabinoid signaling and synaptic function. Neuron 2012;76:70-81.
30. Riebe CJ, Pamplona FA, Kamprath K, Wotjak CT. Fear relief-toward a new conceptual frame work and what endocannabinoids gotta do with it. Neuroscience 2012;204:159-185.
31. McLaughlin RJ, Hill MN, Gorzalka BB. A critical role for prefrontocortical endocannabinoid signaling in the regulation of stress and emotional behavior. Neurosci Biobehav Rev 2014;42: 116-131.
32. Moreira FA, Lutz B. The endocannabinoid system: emotion, learning and addiction. Addict Biol 2008;13:196-212.
33. Ruehle S, Rey AA, Remmers F, Lutz B. The endocannabinoid system in anxiety, fear memory and habituation. J Psychopharmacol 2012;26:23-39.
34. Llorente-Berzal A, Terzian AL, di Marzo V, Micale V, Viveros MP, Wotjak CT. 2-AG promotes the expression of conditioned fear via cannabinoid receptor type 1 on GABAergic neurons. Psychopharmacology 2015;232: 2811-2825.
35. Marsicano G, Wotjak CT, Azad SC, et al. The endogenous cannabinoid system controls extinction of aversive memories. Nature 2002;418:530-534.
36. Dincheva I, Drysdale AT, Hartley CA. FAAH genetic variation enhances fronto-amygdala function in mouse and human. Nat Commun 2015;6:6395.
37. Gray JM, Vecchiarelli HA, Morena M, et al. Corticotropin-releasing hormone drives anandamide hydrolysis in the amygdala to promote anxiety. J Neurosci 2015;35:3879-3892.
38. Evanson NK, Tasker JG, Hill MN, Hillard CJ, Herman JP. Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling. Endocrinology 2010;151:4811-4819.
39. Abush H, Akirav I. Cannabinoids ameliorate impairments induced by chronic stress to synaptic plasticity and short-term memory. Neuropsychopharmacology 2013;38:1521-1534.
40. Hill MN, Patel S, Carrier EJ, et al. Downregulation of endocannabinoid signaling in the hippocampus following chronic unpredictable stress. Neuropsychopharmacology 2005;30;508-515.
41. Qin Z, Zhou X, Pandey NR, et al. Chronic stress induces anxiety via an amygdalar intracellular cascade that impairs endocannabinoid signaling. Neuron 2015;85:1319-1331.
42. Neumeister A. The endocannabinoid system provides an avenue for evidence-based treatment development for PTSD. Depress Anxiety 2013;30:93-96.
43. Papini S, Sullivan GM, Hien DA, Shvil E, Neria Y. Toward a translational approach to targeting the endocannabinoid system in posttraumatic stress disorder: a critical review of preclinical research. Biol Psychol 2015;104:8-18.
44. Ragen BJ, Seidel J, Chollak C, Pietrzak RH, Neumeister A. Investigational drugs under development for the treatment of PTSD. Exp Opin Invest Drugs 2015;24:659-672.
45. Viveros MP, Marco EM, File SE. Endocannabinoid system and stress and anxiety responses. Pharmacol Biochem Behav 2005;81:331-342.
46. Rubino T, Realini N, Castiglioni C, et al. Role in anxiety behavior of the endocannabinoid system in the prefrontal cortex. Cereb Cortex 2008;18:1292-1301.
47. Moreira FA, Aguiar DC, Terzian AL, Guimaraes FS, Wotjak CT. Cannabinoid type 1 receptors and transient receptor potential vanilloid type 1 channels in fear and anxiety-two sides of one coin? Neuroscience 2012;204:186-192.
48. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001;134:845-852.
49. Haller J, et al. Interactions between environmental aversiveness and the anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rats. Psychopharmacology 2009;204:607-616.
50. Chessick CA, Allen MH, Thase M, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev 2006;CD006115.
51. Roncon CM, Biesdorf C, Coimbra NC, et al. Cooperative regulation of anxiety and panic-related defensive behaviors in the rat periaqueductal grey matter by 5-HT1A and mu-receptors. J Psychopharmacol 2013;27:1141-1148.
52. Zhou J, Cao X, Mar AC, et al. Activation of postsynaptic 5-HT1A receptors improve stress adaptation. Psychopharmacology 2014;231:2067-2075.
53. Saito Y, Matsumoto M, Yanagawa Y, et al. Facilitation of fear extinction by the 5-HT(1A) receptor agonist tandospirone: possible involvement of dopaminergic modulation. Synapse 2013;67:161-170.

54. Sprouse JS, Aghajanian GK. Electrophysiological responses of serotoninergic dorsal raphe neurons to 5-HT1A and 5-HT1B agonists. Synapse 1987;1:3-9.
55. Sun YN, Wang T, Wang Y, et al. Activation of 5-HT receptors in the medial subdivision of the central nucleus of the amygdala produces anxiolytic effects in a rat model of Parkinson's disease. Neuropharmacology 2015;95:181-191.
56. Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. CNS Drugs 2013;27:703-716.
57. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res 2005;30:1037-1043.
58. Rock EM, Bolognini D, Limebeer CL, et al. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. Br J Pharmacol 2012;165:2620-2634.
59. Silveira Filho NG, Tufik S. Comparative effects between cannabidiol and diazepam on neophobia, food intake and conflict behavior. Res Commun Psychol Psychiatry Behav 1981;6:25-26.
60. Zuardi AW, Finkelfarb E, Bueno OF, Musty RE, Karniol IG. Characteristics of the stimulus produced by the mixture of cannabidiol with delta 9-tetrahydrocannabinol. Arch Int Pharmacodyn Ther 1981;249:137-146.
61. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. J Pharmacol Exp Ther 1990;253:1002-1009.
62. Moreira FA, Aguiar DC, Guimaraes FS. Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1466-1471.
63. Resstel LB, Joca SR, Moreira FA, Correa FM, Guimaraes FS. Effects of cannabidiol and diazepam on behavioral and cardiovascular responses induced by contextual conditioned fear in rats. Behav Brain Res 2006;172:294-298.
64. Campos AC, Guimaraes FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology (Berl) 2008;199:223-230.
65. Bitencourt RM, Pamplona FA, Takahashi RN. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur Neuropsychopharmacol 2009;18:849-859.
66. Campos AC, Guimaraes FS. Evidence for a potential role for TRPV1 receptors in the dorsolateral periaqueductal gray in the attenuation of the anxiolytic effects of cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:1517-1521.
67. Resstel LB, Tavares RF, Lisboa SF, et al. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. Br J Pharmacol 2009;156:181-188.
68. Soares Vde P, Campos AC, Bortoli VC, et al. Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors. Behav Brain Res 2010;213:225-229.
69. Long LE, Chesworth R, Huang XF. A behavioural comparison of acute and chronic Delta9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. Int J Neuropsychopharmacol 2010;13:861-876.
70. Lemos JI, Resstel LB, Guimaraes FS. Involvement of the prelimbic prefrontal cortex on cannabidiol-induced attenuation of contextual conditioned fear in rats. Behav Brain Res 2010;207:105-111.
71. Casarotto PC, Gomes FV, Resstel LB, Guimaraes FS. Cannabidiol inhibitory effect on marble-burying behaviour: involvement of CB1 receptors. Behav Pharmacol 2010;21:353-358.
72. Gomes FV, Resstel LB, Guimaraes FS. The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. Psychopharmacology (Berl) 2011;213:465-473.
73. Granjeiro EM, Gomes FV, Guimaraes FS, Correa FM, Resstel LB. Effects of intracisternal administration of cannabidiol on the cardiovascular and behavioral responses to acute restraint stress. Pharmacol Biochem Behav 2011;99:743-748.
74. Deiana S, Watanabe A, Yamasaki Y. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Delta(9)-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behaviour. Psychopharmacology (Berl) 2012;219:859-873.
75. Uribe-Marino A, et al. Anti-aversive effects of cannabidiol on innate fear-induced behaviors evoked by an ethological model of panic attacks based on a prey vs the wild snake Epicrates cenchria crassus confrontation paradigm. Neuropsychopharmacology 2012;37:412-421.
76. Stern CA, Gazarini L, Takahashi RN, Guimaraes FS, Bertoglio LJ. On disruption of fear memory by reconsolidation blockade: evidence from cannabidiol treatment. Neuropsychopharmacology 2012;37:2132-2142.
77. Campos AC, Ferreira FR, Guimaraes FS. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. J Psychiatr Res 2012;46:1501-1510.
78. Hsiao YT, Yi PL, Li CL, Chang FC. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. Neuropharmacology 2012;62:373-384.
79. Gomes FV, Resstel LB, Guimaraes FS, et al. Cannabidiol injected into the bed nucleus of the stria terminalis reduces the expression of contextual fear conditioning via 5-HT1A receptors. J Psychopharmacol 2012;26:104-113.
80. El Batsh MM, Assareh N, Marsden CA, Kendall DA. Anxiogenic-like effects of chronic cannabidiol administration in rats. Psychopharmacology (Berl) 2012;221:239-247.
81. Campos AC, Ortega Z, Palazuelos J, et al. The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system. Int J Neuropsychopharmacol 2013;16:1407-1419.
82. Do Monte FH, Souza RR, Bitencourt RM, Kroon JA, Takahashi RN. Infusion of cannabidiol into infralimbic cortex facilitates fear extinction via CB1 receptors. Behav Brain Res 2013;250:23-27.
83. Campos AC, de Paula Soares V, Carvalho MC, et al. Involvement of serotonin-mediated neurotransmission in the dorsal periaqueductal gray matter on cannabidiol chronic effects in panic-like responses in rats. Psychopharmacology (Berl) 2013;226:13-24.
84. Almeida V, Levin R, Peres FF, et al. Cannabidiol exhibits anxiolytic but not antipsychotic property evaluated in the social interaction test. Prog Neuropsychopharmacol Biol Psychiatry 2013;41:30-35.
85. Gomes FV, Alves FH, Guimaraes FS, et al. Cannabidiol administration into the bed nucleus of the stria terminalis alters cardiovascular responses induced by acute restraint stress through 5-HT(1)A receptor. Eur Neuropsychopharmacol 2013;23:1096-1104.
86. Twardowschy A, Castiblanco-Urbina MA, Uribe-Marino A, et al. The role of 5-HT1A receptors in the anti-aversive effects of cannabidiol on panic attack-like behaviors evoked in the presence of the wild snake *Epicrates cenchria crassus* (Reptilia, Boidae). J Psychopharmacol 2013;27:1149-1159.
87. Fogaca MV, Reis FM, Campos AC, Guimaraes FS. Effects of intra-prelimbic prefrontal cortex injection of cannabidiol on anxiety-like behavior: involvement of 5HT1A receptors and

previous stressful experience. Eur Neuropsychopharmacol 2014;24:410-419.
88. Nardo M, Casarotto PC, Gomes FV, Guimaraes FS. Cannabidiol reverses the mCPP-induced increase in marble-burying behavior. Fundam Clin Pharmacol 2014;28:544-550.
89. da Silva JA, Biagioni AF, Almada RC, et al. Dissociation between the panicolytic effect of cannabidiol microinjected into the substantia nigra, pars reticulata, and fear-induced antinociception elicited by bicuculline administration in deep layers of the superior colliculus: The role of CB-cannabinoid receptor in the ventral mesencephalon. Eur J Pharmacol 2015;758:153-163.
90. Guimaraes FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. Psychopharmacology (Berl) 1990;100:558-559.
91. Bandler R, Shipley MT. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? Trends Neurosci 1994;17:379-389.
92. Nashold BS, Jr, Wilson WP, Slaughter DG. Sensations evoked by stimulation in the midbrain of man. J Neurosurg 1969;30:14-24.
93. Walker DL, Miles LA, Davis M. Selective participation of the bed nucleus of the stria terminalis and CRF in sustained anxiety-like versus phasic fear-like responses. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:1291-1308.
94. Sierra-Mercado D, Padilla-Coreano N, Quirk GJ. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology 2011;36:529-538.
95. Schenberg LC, Bittencourt AS, Sudre EC, Vargas LC. Modeling panic attacks. Neurosci Biobehav Rev 2001;25;647-659.
96. Thomas A, Burant A, Bui N, Graham D, Yuva-Paylor LA, Paylor R. Marble burying reflects a repetitive and perseverative behavior more than novelty-induced anxiety. Psychopharmacology (Berl) 2009;204;361-373.
97. Suzuki A, Josselyn SA, Frankland PW, et al. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci 2004;24:4787-4795.
98. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology (Berl) 1982;76: 245-250.
99. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. Eur J Pharmacol 1974;28:172-177.
100. Zuardi AW, Cosme RA, Graeff FG, Guimaraes FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. J Psychopharmacol 1993;7:82-88.
101. Martin-Santos R, Crippa JA, Batalla A, et al. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr Pharm Design 2012;18:4966-4979.
102. Crippa JA, Zuardi AW, Garrido GE, et al. Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology 2004;29:417-426.
103. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010;35:764-774.
104. Crippa JA, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol 2011;25: 121-130.
105. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology 2011;36:1219-1226.
106. Das RK, Kamboj SK, Ramadas M, et al. Cannabidiol enhances consolidation of explicit fear extinction in humans. Psychopharmacology 2013;226:781-792.
107. Hindocha C, Freeman TP, Schafer G, et al. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. Eur Neuropsychopharmacol 2015;25:325-334.
108. Borgwardt SJ, Allen P, Bhattacharyya S, et al. Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biol Psychiatry 2008;64:966-973.
109. Fusar-Poli P, Crippa JA, Bhattacharyya S. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry 2009;66:95-105.
110. Fusar-Poli P, Allen P, Bhattacharyya S. Modulation of effective connectivity during emotional processing by Delta 9-tetrahydrocannabinol and cannabidiol. Int J Neuropsychopharmacol 2010;13:421-432.
111. Rubia K, Russell T, Overmeyer S, et al. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage 2001;13:250-261.
112. Falconer E, Allen A, Felmingham KL, Williams LM, Bryant RA. Inhibitory neural activity predicts response to cognitive-behavioral therapy for posttraumatic stress disorder. J Clin Psychiatry 2013;74:895-901.
113. Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J Affect Disord 2014;167:336-342.
114. Patel R, Spreng RN, Shin LM, Girard TA. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev 2012;36:2130-2142.
115. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology 2010;35: 1879-1885.
116. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry 2008;192:306-307.
117. Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. Br J Psychiatry 2010;197:285-290.
118. Demirakca T, Sartorius A, Ende G, et al. Diminished gray matter in the hippocampus of cannabis users: possible protective effects of cannabidiol. Drug Alcohol Depend 2011;114:242-245.
119. Niesink RJ, van Laar MW. Does cannabidiol protect against adverse psychological effects of THC? Front Psychiatry 2013;4:130.
120. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. J Psychoactive Drugs 2014;46:73-77.
121. Passie T, Emrich HM, Karst M, Brandt SD, Halpern JH. Mitigation of post-traumatic stress symptoms by Cannabis resin: a review of the clinical and neurobiological evidence. Drug Test Anal 2012;4:649-659.

# REFERENCE #13

Cannabis and Cannabinoid Research
Volume 3.1, 2018
DOI: 10.1089/can.2018.0022

Cannabis and Cannabinoid Research
Mary Ann Liebert, Inc. publishers

REVIEW Open Access

# Emerging Evidence for Cannabis' Role in Opioid Use Disorder

Beth Wiese[1,2] and Adrianne R. Wilson-Poe[2,*]

## Abstract

**Introduction:** The opioid epidemic has become an immense problem in North America, and despite decades of research on the most effective means to treat opioid use disorder (OUD), overdose deaths are at an all-time high, and relapse remains pervasive.

**Discussion:** Although there are a number of FDA-approved opioid replacement therapies and maintenance medications to help ease the severity of opioid withdrawal symptoms and aid in relapse prevention, these medications are not risk free nor are they successful for all patients. Furthermore, there are legal and logistical bottlenecks to obtaining traditional opioid replacement therapies such as methadone or buprenorphine, and the demand for these services far outweighs the supply and access. To fill the gap between efficacious OUD treatments and the widespread prevalence of misuse, relapse, and overdose, the development of novel, alternative, or adjunct OUD treatment therapies is highly warranted. In this article, we review emerging evidence that suggests that cannabis may play a role in ameliorating the impact of OUD. Herein, we highlight knowledge gaps and discuss cannabis' potential to prevent opioid misuse (as an analgesic alternative), alleviate opioid withdrawal symptoms, and decrease the likelihood of relapse.

**Conclusion:** The compelling nature of these data and the relative safety profile of cannabis warrant further exploration of cannabis as an adjunct or alternative treatment for OUD.

**Keywords:** cannabis; opioid addiction; opioid treatment; relapse prevention

## Introduction

The opioid epidemic has become an increasingly pressing problem with an estimated 26–36 million people abusing opioids around the world.[1] At the time of this publication, the Centers for Disease Control reports that 115 people die every day of an opioid related cause in the United States, and more than 33,000 people lost their lives to an accidental opioid overdose in the United States in 2015 alone.[1–4] The United States consumes 80% of the world's supply of prescription opioid analgesics (POAs), and opioid prescriptions have climbed by 300% since 1991.[5] The rise in opioid prescriptions has also widened the demographic of individuals dying from opioid overdose; historically, overdose was most prevalent in urban, minority adolescent males; however, today these lethal effects are similar across race, gender, socioeconomic status, and geography.[7–11] The spike in prescriptions has also directly contributed to an increase in the number of first-time consumers of illicit opioids (heroin, which is commonly laced with fentanyl or its analogs), which has continued to climb since the mid 1990's.[6] Patients who become physically dependent upon POAs frequently switch to illicit opioids because POAs are more costly and/or difficult to obtain.[3,8,12,13] However, ease of access is a dangerous tradeoff for the lethal risk that is associated

[1]Department of Psychology, University of Missouri–St. Louis, St. Louis, Missouri.
[2]Department of Anesthesiology, Pain Center, Washington University School of Medicine, St. Louis, Missouri.

*Address correspondence to: Adrianne R. Wilson-Poe, MA, Department of Anesthesiology, Pain Center, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8054, St. Louis, MO 63110, E-mail: poea@anest.wustl.edu

with synthetic opioids. Fentanyl, for instance, is 100 times more potent than morphine, which partially explains why there was a 250% increase in synthetic opioid mortality between 2012 and 2015.[14,15]

This unprecedented public health crisis warrants the investigation of novel sustainable interventions which would directly address the current opioid misuse crisis, complement current treatment strategies, and prevent future misuse through alternative first line analgesics.

## Mechanistic Interactions between Cannabis and Opioids

The endocannabinoid and opioidergic systems are known to interact in many different ways, from the distribution of their receptors to cross-sensitization of their behavioral pharmacology. Cannabinoid-1 (CB1) receptors and mu opioid receptors (MORs) are distributed in many of the same areas in the brain, including but not limited to the periaqueductal gray,[16,17] locus coeruleus,[18,19] ventral tegmental area (VTA), nucleus accumbens, prefrontal cortex (PFC),[20] central amygdala (CeA), bed nucleus of stria terminalis (BNST),[21] caudate putamen (CP), substantia nigra, dorsal hippocampus, raphe nuclei, and medial basal hypothalamus.[22] The extent of this overlapping expression and frequent colocalization of the CB1 and MOR provide clear morphological underpinnings for interactions between the opioid and cannabinoid systems in reward and withdrawal.[19,23]

There is a bidirectional relationship between MORs and CB1 receptors in the rewarding properties of drugs of misuse.[20,24–28] That is, modulation of the CB1 receptor has profound effects on the rewarding properties of opioids, and *vice versa*. For example, MOR and CB1 receptors are reciprocally involved in the development of drug-induced conditioned place preference (CPP). Coadministration of a cannabinoid antagonist and morphine attenuates the development of morphine CPP,[26] and coadministration of an opioid antagonist blocks tetrahydrocannabinol (THC)-induced CPP.[25] Interestingly, microinjections of CB1 agonists into the medial PFC creates an aversion to doses of morphine that are normally rewarding (CPP), while CB1 antagonism in this brain region creates a rewarding effect of subthreshold morphine doses.[24] In addition, administration of cannabinoids to MOR knockout (KO) mice produces a weaker CPP compared to wild-type animals,[22] reviewed in Wills and Parker.[27] This mutual involvement in reward is at least partially mediated by presynaptic cannabinoid and opioid disinhibition of dopamine neurons in the VTA, a well-characterized mechanism in the rewarding properties of drugs of misuse.[20] Although these mechanisms have not been well studied in humans, one study has found CB1 upregulation in the reward pathway of individuals who use opioids, which supports a role for the endocannabinoid system in the development of opioid misuse.[29]

There is abundant support for the role of CB1 receptors in the rewarding effects of opioids and the amelioration of tolerance. However, the effects of endogenous and exogenous cannabinoids in opioid withdrawal are somewhat paradoxical: endogenous cannabinoids seem to have no role in somatic withdrawal,[27,30–32] yet exogenous CB1 agonists readily alleviate somatic symptoms such as escape jumps, diarrhea, weight loss, and paw tremors.[28,33,34] Endogenous cannabinoid tone within the amygdala is also involved in the affective component of opioid withdrawal, as blockade of CB1 receptors in the CeA or BNST ameliorates opioid withdrawal.[21] The kappa opioid receptor (KOR) system may also play a role in cannabis' impact on the affective opioid withdrawal, given its pivotal contributions to dysphoria and negative effect.[35] However, both KOR agonism (with U50, 488H[30]) and KOR antagonism (naloxone[31,32]) have both been shown to attenuate conditioned place aversion in CB1 KO mice.[30] These contradicting data highlight the need for additional mechanistic insights into the involvement of the CB1 receptor in opioid reward and withdrawal.

## Cannabis as a First Line Analgesic

The primary use for both prescription opioids and cannabis is for analgesia. Currently, up to 90% of patients in state-level medical cannabis registries list chronic pain as their qualifying condition for the medical program.[36] In an exhaustive review, the National Academies of Science and Medicine recently confirmed the efficacy of cannabis for chronic pain in adults.[36] Interestingly, when given access to cannabis, individuals currently using opioids for chronic pain decrease their use of opioids by 40–60% and report that they prefer cannabis to opioids.[37–42] Patients in these studies reported fewer side effects with cannabis than with their opioid medications (including a paradoxical improvement in cognitive function) and a better quality of life with cannabis use, compared to opioids. Despite the vast array of cannabis products and administration routes used by patients in states with medical cannabis laws, cannabis has been consistently shown to reduce the opioid dose needed to achieve desirable pain relief.[41,43]

One of the mechanisms that may explain the opioid sparing effects of cannabis is its ability to produce

synergistic analgesia.[44–46] In humans, subanalgesic doses of THC and morphine are equally unsuccessful at reducing the sensory or affective components of pain; however, when the same doses of THC and morphine are coadministered, they produce a significant reduction in the affective component of pain.[47] These synergistic effects are also observed when patients using opioids for pain vaporize whole-plant cannabis, as opposed to experimentally administered isolated THC.[48] Adjunct whole plant cannabis has no effect on the pharmacokinetics of opioids, which further supports a synergistic mechanism behind the opioid sparing and enhanced analgesia produced by cannabis.[48] Furthermore, in pre-clinical models, coadministration of opioids and cannabinoids attenuates the development of opioid tolerance.[49,50]

Combined, these clinical and pre-clinical data suggest that analgesic synergy produced by coadministered cannabis and opioids could be harnessed to achieve clinically relevant pain relief at doses that would normally be subanalgesic. This strategy could have significant impacts on the opioid epidemic, given that it could entirely prevent two of the hallmarks of opioid misuse: dose escalation and physical dependence.

Because patients report substituting cannabis for several types of pharmaceutical drugs, including opioids, benzodiazepines, and antidepressants,[51] analgesic synergy may not entirely explain the opioid-sparing effects of cannabis in pain patients. Economic and lifestyle considerations may also play a pivotal role in opioid sparing and substitution. Patients report that their reasons for substituting cannabis for other medications include less severe side effects, less withdrawal potential, ease of access, and better symptom management for their conditions.[52]

Although there is insufficient clinical literature to support the use of cannabis as a treatment for acute pain, there is a long-standing body of pre-clinical evidence that demonstrates the antinociceptive effects of cannabinoids in pain-free, drug-naive animals.[17,49,53–57] The mechanisms of cannabinoid antinociception are remarkably similar to those of opioid analgesics. Both the CB1 and MOR are G-protein coupled receptors, and agonist-initiated disinhibition of GABA release in the descending pain pathway is just one example of overlapping antinociceptive mechanisms between these drugs.[17,23,58–62] Evidence supporting the role of cannabis in acute, nonsevere pain management could lead to a substantial reduction in opioid prescription rates, thereby eliminating patient exposure to the risks of opioid dose escalation and physical dependence. This critical gap in the clinical literature and potential clinical impacts of this therapy warrants further exploration of the efficacy of cannabis for acute pain relief.

## Current Opioid Use Disorder Therapies and Their Shortcomings

The most prominent and pervasive problem in opioid use disorder (OUD) treatment is the prevention of drug relapse, which is extremely common during acute withdrawal (detoxification), as well as during protracted recovery after physical withdrawal symptoms have subsided.[63–66] Abstinence-based protocols are particularly ineffective, as 85% of individuals relapse within 12 months of the initiation of treatment.[65] In-patient residential treatment facilities do not appear to improve abstinence-based therapy, as relapse rates in this paradigm are as high as 80%, when measured 2 years after treatment initiation.[67] Compared to abstinence, opioid replacement and medication-assisted therapies, which began in the 1960s, are more efficacious for relapse prevention; however, there are currently only four FDA-approved medications for the treatment of OUD.[68–71] Off-label prescription medications such as benzodiazepines and antiemetics are also common, but these therapies are largely directed at symptom management during acute detoxification rather than relapse prevention.[72] In this review, we focus on the most widely used OUD therapies, their shortcomings, and the bottlenecks to accessing them.[11]

Methadone, a full MOR agonist, was approved by the FDA in 1974 to aid in opioid cessation.[9,73] Individuals enrolled in consistent dose methadone maintenance programs are more likely to stop using nonprescribed opioids than individuals not enrolled in the maintenance program.[74] Although methadone has an encouraging safety profile,[75] it carries some risk for misuse and mortality when the dose exceeds the patient's level of tolerance.[76,77] Withdrawal symptoms from methadone mimic those of other opioids when stopped abruptly or tapered too quickly, and these symptoms last up to 3 weeks longer than withdrawal from other opioids.[9,78,79] There are only 1590 methadone distributers in the United States, which are highly regulated clinics that are concentrated in urban areas, creating geographical disparities in OUD treatment.[10,11,79] In addition to geographical barriers, these clinics frequently have stringent and stigmatizing compliance requirements, such as daily visits and frequent urine screenings for illicit drugs.[11,80] Although these barriers to treatment could potentially be addressed

through concerted efforts to expand access, 40% of patients still relapse within 1 year of initiating methadone therapy.[67]

Buprenorphine (Subutex) is a partial MOR agonist and KOR antagonist that can reduce withdrawal symptoms, cravings, and additional opioid use.[76,81,82] The inclusion of naloxone in some buprenorphine formulations (Suboxone, Zubsolv) is intended to reduce misuse by precipitating withdrawal when it is used intravenously,[82,83] and despite the presence of naloxone, there is still some risk for misuse and overdose.[77,83,84] The inclusion of naloxone can also induce withdrawal when administered too soon after the most recent dose of other opioids.[63,67,85]

Unlike methadone, Suboxone offers a primary care approach to medication-assisted therapy, as it can be dispensed by a pharmacy rather than a specialized clinic.[86,87] However, only 3% of physicians possess the additional Drug Enforcement Agency credentials required to prescribe buprenorphine,[76,88] and there are strict limits on the number of patients they are permitted to serve.[89] Buprenorphine-licensed physicians also tend to be concentrated in larger cities, leaving 46.8% of counties in the United States, especially rural areas and the Midwest, with a shortage in convenient access to these treatment options.[88,90,91] While long-term treatment retention with buprenorphine or Suboxone is not as well characterized as methadone, a Swedish study has shown retention rates of up to 75% following a year of buprenorphine/Suboxone treatment.[92] However, a 24-week clinical trial in the United States reveals that buprenorphine retention is only 46%.[93]

Evidence suggests that the most effective tool for relapse prevention is medication-assisted pharmacotherapy, combined with social support.[76,78,94,95] Because of the overwhelming evidence that supports this concurrent treatment model, there is little rationale to deviate from this approach. However, expanded access to these therapies is highly warranted, as are novel and alternative therapies which improve efficacy, diminish geographical disparities, and eliminate the need for specialty physicians.[96]

## Cannabis During Acute Opioid Withdrawal

The first barrier to overcoming OUD is getting patients through the acute withdrawal period, or detoxification. Although pharmacotherapies such as methadone and buprenorphine are largely successful and widely utilized for this purpose, there are shortcomings to this approach, which are highlighted above.[9,76,78,80,82,83,87,89–91,97] In May of 2018, the FDA approved the use of lofexidine, an alpha-2 adrenergic receptor agonist for acute (14 day) opioid withdrawal. Lofexidine provides substantially more symptom relief than placebo; however, the comparative efficacy of lofexidine in combination with long-acting opioid agonists or opioid antagonists is still being characterized.[71,98–100]

There is also nascent evidence that suggests that cannabis may be an efficacious tool during the acute opioid withdrawal period. Numerous pre-clinical studies have shown that cannabis and cannabinoids decrease opioid withdrawal symptoms.[6,33,34,97,101–103] Although this evidence supports the use of cannabinoids as a possible treatment in OUD treatment,[28] conflicting evidence demonstrates that CB1 agonism increases the rewarding properties of opioids[22,102] and may actually increase the severity of opioid withdrawal symptoms.[18,104] These conflicting data highlight the need for a mechanistic characterization of CB1 agonism as a therapeutic target for opioid withdrawal, a need that is further substantiated by the pharmacology of CB1 antagonism. For instance, some studies show that acute administration of SR-141716A, a CB1 antagonist, can reduce opioid withdrawal; however, this effect is profoundly affected by the experimental conditions.[22,105] Because this effect can be recapitulated in CB1 KO mice, CB1 antagonism only partially mediates these effects.[102] To complicate the story further, the administration of cannabidiol (CBD), a very promiscuous phytocannabinoid with at least a dozen mechanisms of action, also alleviates naloxone-precipitated withdrawal in morphine tolerant rats.[106–112]

Although the mechanisms by which cannabinoids alleviate opioid withdrawal are complex and unclear, some reports suggest that cannabis may alleviate opioid withdrawal in humans.[18,113] For instance, patients engaging in medication-assisted detoxification from opioids reported using cannabis when opioid maintenance doses were not high enough to prevent withdrawal and cravings.[114] However, some individuals reported that cannabis was often ineffective and sometimes worsened overall severity of the withdrawal symptoms. Because the phytochemical makeup and cannabinoid content of cannabis have a significant effect on subjective human experiences,[115] it is plausible that these variable experiences are the result of variable phytochemistry in cannabis products that are self-selected by study participants. Unfortunately, blinded, placebo-controlled clinical trials evaluating the efficacy of cannabis, either alone or as an adjunct therapy for acute opioid withdrawal, are lacking. This is not entirely surprising, given cannabis' status as a Schedule I substance in the

United States, which precludes federal funding to investigate cannabis as a medication-assisted therapy.

Unlike whole-plant cannabis, dronabinol, an FDA-approved analog of THC, has been evaluated for opioid withdrawal relief in a placebo-controlled study in patients receiving the opioid antagonist naltrexone. Low-dose adjunct dronabinol improved the tolerability of symptoms such as insomnia, reduced appetite, and reduced energy levels during opioid detoxification, whereas adverse events such as tachycardia were reported at higher dronabinol doses.[113,116,117] In many studies, cannabinoids were safe and tolerable when coadministered with an opioid or opioid replacement medication.[47,113,118–120] However, the comparative efficacy of dronabinol or other cannabinoids versus traditional replacement therapies such as methadone or buprenorphine remains to be elucidated. Given the efficacy and tolerability of Sativex (a whole-plant cannabis derivative) for pain and spasticity, investigation of adjunct Sativex for opioid withdrawal is warranted.[121–123]

Like opioids, chronic cannabis exposure induces the development of tolerance, physical dependence, and withdrawal symptoms during abstinence. Patients commonly report that cannabis withdrawal symptoms, most commonly anger, aggression, irritability, anxiety, decreased appetite, weight loss, restlessness, and sleeping difficulties,[124–129] are similar to those produced by nicotine withdrawal.[129] Comparatively, the magnitude and severity of cannabis withdrawal are significantly and substantially more benign than opioid withdrawal.[20,126] In addition, and unlike opioids, cannabinoid withdrawal and subsequent relapse are nonlethal after periods of abstinence. The reduced intensity of cannabinoid withdrawal symptoms compared to opioids could at least partially be explained by the prolonged period of metabolization of cannabinoids in the body,[102] contributing to the mounting support for cannabis as a harm-reduction tool to combat OUD.

## Cannabis as a Harm Reduction Tool in OUD

Pre-clinical evidence suggests that the CB1 receptor plays a critical role in opioid reward. Cannabinoid antagonism reduces the rewarding properties of opioids and prevents reinstatement of drug seeking.[105,130,131] However, these effects were not reproducible in human clinical trials.[132–134] Unlike CB1 antagonism, CB1 agonism may play a role in OUD treatment. Several studies have shown that adjunct cannabis decreases opioid consumption or prevents opioid dose escalation.[37–42,121,135] Although these findings are promising, several other studies have shown that cannabis use either has no impact on opioid consumption or may increase nonmedical opioid use.[136–138]

The mechanisms underlying cannabis alteration of opioid consumption are yet to be determined; however, there is significant pre-clinical evidence which suggests that CBD, one of the most prevalent cannabinoid molecules in cannabis, plays a critical role. CBD does not have reinforcing effects in rodents, which supports its low potential for misuse.[16,139] CBD has been shown to reduce the rewarding aspects of multiple drugs of abuse, such as cocaine, amphetamine,[16] and nicotine.[140] Administration of CBD also attenuates morphine CPP and cue-induced reinstatement of heroin self-administration in rats, without creating any aversive or rewarding effects on its own.[106,141–143]

These findings provide promising rationale for the use of CBD in opioid relapse prevention in humans. In fact, pilot clinical studies have shown that in individuals recently abstinent from heroin, CBD reduces heroin craving.[142] This effect occurs as soon as 1 h after administration and lasts for up to 7 days. Adjunct CBD appears to be safe and tolerable, as 400 and 800 mg oral CBD administration does not intensify the effects of intravenous fentanyl or create any adverse effects.[118] Because CBD is neither intoxicating nor rewarding and has an extremely large therapeutic window and impressive safety profile, the use of CBD to inhibit opioid craving has great therapeutic potential.

Adjunct cannabis use alongside current treatment strategies could help to improve the number of individuals engaging in OUD treatment, as well as increase treatment retention rates. Both dronabinol and intermittent whole-plant cannabis appear to increase the length of time patients remain in treatment for OUD.[6,113] However, chronic cannabis consumption during naltrexone treatment was ineffective at improving treatment retention, highlighting the need for further research into the dose and frequency of cannabis use in OUD treatment retention and relapse prevention.[144] Although the ubiquitous and ever-growing regulated cannabis markets across North America could potentially address the aforementioned shortcomings in OUD treatment accessibility and retention, there are currently very few addiction and recovery centers that have embraced concurrent social support and cannabis-assisted OUD treatment.[51] This is unsurprising given the lack of empirical evidence to support this approach, and the lack of federal research funding that would support this work.

In addition to the clinical and experimental observations outlined above, epidemiological investigations in

U.S. states with legal cannabis have provided insight into the promising role for cannabis in the opioid crisis. The implementation of both medical and adult-use cannabis laws appears to have a significant impact on opioid consumption and overdose. These states experience a 23% reduction in nonfatal opioid overdoses, as measured at hospital emergency departments.[145] By analyzing death certificates, Bachhuber et al. found a 24% reduction in the annual rate of fatal opioid overdoses in the first year following medical cannabis legalization,[146] an effect that gets larger the longer a state has had legal cannabis (33% in California, which has had medical use since 1996 and the lowest rate of opioid overdose fatalities in the country).[146,147] This finding was also seen in data from the FARS, which demonstrates a similar drop in mortalities of opioid positive automobile accidents in states with implemented cannabis legalization for individuals aged 21–40.[148] The mechanisms underlying cannabis' ability to reduce opioid hospitalization and mortality are unclear; however, analysis of the Medicare Part D prescription drug program has unveiled the possibility that cannabis may be serving as an analgesic alternative to opioids for individuals living in these states.[149] The number of filled POAs is substantially lower in states with the most liberal cannabis laws, where there are 3.742 million fewer daily doses than in states with the most prohibitive laws.[150]

These epidemiological impacts are not exclusive to opioid prescriptions, hospitalizations, and mortality; the U.S. economy could also benefit from expanded cannabis legalization. Opioids cost patients and insurance companies upwards of 2.6 billion dollars in healthcare costs annually.[151] While cannabis is still federally illegal, and in most cases dispensary purchases are not eligible to be covered under any healthcare insurance plan, states with legalized cannabis have seen significant decreases in Medicare Part D prescription drug spending, including, but not limited to, prescription opioids.[149,152–155] Reductions in spending from Medicare Part D were over $165 million dollars.[149] If cannabis were removed from Schedule I of the Controlled Substance Act and more patients had access to cannabis, savings from pharmaceutical costs incurred by the Medicare Part D prescription plan are projected to continue to climb.[149]

## Shortcomings of Cannabis in Medication-Assisted Therapy

Although the literature thoroughly supports the safety and tolerability of cannabis,[38,118,142,156] there is conflicting evidence for its efficacy as a treatment for opioid misuse. Throughout the history of methadone administration, patients have reported that cannabis provides relief from opioid withdrawal symptoms, as well as breakthrough pain and anxiety.[119] However, other evidence demonstrates that cannabis does not relieve withdrawal symptoms for individuals undergoing methadone tapering, and some participants even reported increased severity of their withdrawal symptoms.[104] All the participants in the latter study procured their own cannabis and reported smoking as the route of administration. Because the dose of cannabinoids and phytochemical makeup of whole-plant cannabis have significant impacts on physiological responses (such as tachycardia) and subjective experiences (such as anxiety), additional research is needed to characterize maximally efficacious treatment protocols.[116,157] When used to treat opioid withdrawal symptoms, undesirable side effects also occur in a dose-dependent manner for the FDA-approved cannabinoid dronabinol.[113] The homogenous and consistent formulation of this pharmaceutical combined with the logistical ease of prescribing the drug may make it more feasible than whole-plant cannabis for clinical trials on cannabinoid alleviation of opioid withdrawal symptoms and relapse prevention.

Despite the promising results of reducing or maintaining a consistent opioid dose, it is plausible that the substitution of one rewarding substance (opioids) for another (THC) could be problematic, leading to cannabis use disorder (CUD). In 2016, ~1.4–2.9% of adults over the age of 18 in the United States met criteria for CUD.[79] With revisions to the criteria of substance use disorders in 2013, ~19% of individuals who use cannabis throughout their lifetime would eventually meet the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for CUD.[153] The interpersonal or employment hardships experienced by these individuals that resulted in the meeting of DSM criteria may have simply been due to the legality of cannabis use; that is, a false CUD diagnosis is less likely to occur in the postprohibition era, when patients are no longer breaking the law.

Risks of CUD seem to be correlated with higher THC concentrations,[153] which is a valid concern in legal markets where average THC potency is upward of 20%.[158] Recreational users of cannabis have historically consumed cultivars higher in THC and lower in CBD, due to the desired intoxicating effects of THC.[38] Medical users, however, have turned to cultivars higher in

CBD and lower in THC in an attempt to optimize the medicinal benefits of cannabis.[38,153] Although misuse potential is a valid concern, it is notable that the misuse liability of cannabis is very low.[159] One possible approach to alleviate the concern of misuse is the concurrent administration of opioid antagonists. This approach seems to reduce the rewarding properties, but not the hyperphagia or withdrawal-relieving properties of THC.[160–164] These data suggest that combined cannabis and opioid-antagonist therapy could be an effective tool against OUD, while also minimizing the risk for CUD. Because cannabis does not carry the risk of fatal overdose, the use of cannabis as a harm-reduction treatment in the opioid epidemic warrants further investigation.

## Summary and Future Directions

The opioid overdose epidemic is arguably the worst public health crisis in U.S. history. At the time of this publication, more people are dying than at the peak of the AIDS epidemic, and for the first time, drug overdoses outnumber automobile and handgun deaths.[165] A continental crisis of this magnitude warrants the immediate implementation of novel strategies that prevent opioid misuse, overdose, and death.

Growing pre-clinical and clinical evidence appears to support the use of cannabis for these purposes. The evidence summarized in this article demonstrates the potential cannabis has to ease opioid withdrawal symptoms, reduce opioid consumption, ameliorate opioid cravings, prevent opioid relapse, improve OUD treatment retention, and reduce overdose deaths. Cannabis' greatest potential to positively impact the opioid epidemic may be due to its promising role as a first line analgesic in lieu of or in addition to opioids. The comparative efficacy of cannabis alone or in conjunction with current medication-assisted OUD therapies is not well characterized. However, no other intervention, policy, pharmacotherapy, or treatment paradigm has been as impactful as cannabis legislation has been on the rates of opioid consumption, overdose, and death.

Many of the barriers that prevent people from accessing traditional OUD treatment do not apply to cannabis therapy, and access to cannabis medicine is rapidly growing as more U.S. states roll back prohibition. However, a major barrier in universal patient access and improvement in the opioid epidemic is cannabis' status as a Schedule I controlled substance.[166]

Undoubtedly, more high-quality clinical evidence is needed to further support the use of cannabis to combat OUD; however, federal grant funding that would support these types of clinical trials is currently outside the scope of interest of the National Institutes of Health (because of Schedule I, cannabis is federally considered to have no medical benefit). Patients, healthcare providers, and regulating bodies would all greatly benefit from additional evidence that fills in massive gaps in the knowledge base about the utility of cannabis for OUD treatment: dosing, cannabinoid content and ratios, bioavailability, contraindications, misuse liability, route of administration, and many other questions remain. Even the clinical work that has been conducted thus far may have little validity in the modern landscape of legalized cannabis; all federally-funded cannabis research in the United States is conducted using a single source of cannabis (NIDA drug supply), which is notoriously low in potency and quality, and does not resemble the staggering phytochemical variability in whole-plant cannabis products in regulated state markets.[36] These barriers to research funding and access to "real world" cannabis for clinical research directly contribute to our inability to address the opioid epidemic with what appears to be a safe and efficacious tool.

In light of the evidence presented in this article, and despite a lack of FDA approval, some U.S. states and private treatment centers have already begun to include cannabis as a part of OUD treatment protocols. The state of New Jersey recently added OUD to their list of qualifying conditions for participation in the state's medical cannabis program.[167,168] Some private treatment centers are also citing the benefits of harm reduction, which greatly outweigh the risks of cannabis use during the first 28 days of recovery, a critical time period for patient survival.[76]

Many clinicians remain skeptical of cannabis as a viable treatment option, either due to the stigma surrounding cannabis use or the belief that there is not enough clinical evidence for them to feel confident providing patients with cannabis recommendations.[169] This is unsurprising, given that 85% of recent medical school graduates still receive no education whatsoever about cannabis throughout their training, residencies, or fellowships.[170] As the evidence in this field accumulates, it will be critically important to widen opportunities for clinicians to participate in Continuing Medical Education programs, which include the harm reduction and medical benefits that cannabis could provide. Evidence-based opioid prescription and cannabis recommendation practices are a critical component of continuing education, so that clinicians can continue to uphold their Hippocratic oaths to "do no harm."

## Acknowledgment

Supported by grant funding from the National Institute on Drug Abuse to A.W.-P. (K99DA041467).

## Author Disclosure Statement

No competing financial interests exist.

## References

1. Control CfD. Centers for Disease Control and Prevention Understanding the Epidemic 2017. Available at: https://www.cdc.gov/drugoverdose/epidemic (accessed October 12, 2017).
2. DuPont RL. The opioid epidemic is an historic opportunity to improve both prevention and treatment. Brain Res Bull. 2018;138:112–114.
3. Seth P, Scholl L, Rudd RA, et al. Overdose deaths involving opioids, cocaine, and psychostimulants—United States, 2015–2016. MMWR Morb Mortal Wkly Rep. 2018;67:349–358.
4. National Academies of Sciences, Engineering, and Medicine. Pain management and the opioid epidemic: balancing societal and individual benefits and risks of prescription opioid use. National Academies Press: Washington, DC, 2017.
5. Blum K, Gold MS, Jacobs W, et al. Neurogenetics of acute and chronic opiate/opioid abstinence: treating symptoms and the cause. Front Biosci (Landmark Ed). 2017;22:1247–1288.
6. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience. 2013;248:637–654.
7. Rudd RA, Aleshire N, Zibbell JE, et al. Increases in drug and opioid overdose deaths—United States, 2000–2014. Am J Transplant. 2016;16:1323–1327.
8. Cicero TJ, Ellis MS, Surratt HL, et al. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry. 2014;71:821–826.
9. Yarmolinsky A, Rettig RA. Federal regulation of methadone treatment. National Academies Press: Washington, DC, 1995.
10. Substance Abuse and Mental Health Services Administration. Medication-assisted treatment for substance use disorders: Division of Pharmacologic Therapies. Available at: https://dpt2.samhsa.gov/treatment/directory.aspx (accessed October 12, 2017).
11. Huhn AS, Tompkins DA, Dunn KE. The relationship between treatment accessibility and preference amongst out-of-treatment individuals who engage in non-medical prescription opioid use. Drug Alcohol Depend. 2017;180:279–285.
12. Wallace MJ, Wiley JL, Martin BR, et al. Assessment of the role of CB1 receptors in cannabinoid anticonvulsant effects. Eur J Pharmacol. 2001;428:51–57.
13. Cicero TJ, Ellis MS, Harney J. Shifting patterns of prescription opioid and heroin abuse in the United States. N Engl J Med. 2015;373:1789–1790.
14. Centers for Disease Control and Prevention. Increase in overdose deaths involving synthetic opioids other than methadone linked to increase in supply of fentanyl in PBSS states. 2017. Available at: https://www.cdc.gov/drugoverdose/pdf/pbss/PBSS-Report-072017.pdf (accessed October 12, 2017).
15. Wolff RF, Aune D, Truyers C, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Curr Med Res Opin. 2012;28:833–845.
16. Parker LA, Burton P, Sorge RE, et al. Effect of low doses of Δ9-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats. Psychopharmacology (Berl). 2004;175:360–366.
17. Wilson-Poe AR, Pocius E, Herschbach M, et al. The periaqueductal gray contributes to bidirectional enhancement of antinociception between morphine and cannabinoids. Pharmacol Biochem Behav. 2013;103:444–449.
18. Gossop M, Battersby M, Strang J. Self-detoxification by opiate addicts: a preliminary investigation. Br J Psychiatry. 1991;159:208–212.
19. Scavone JL, Mackie K, Van Bockstaele EJ. Characterization of cannabinoid-1 receptors in the locus coeruleus: relationship with mu-opioid receptors. Brain Res. 2010;1312:18–31.
20. López-Moreno JA, López-Jiménez A, Gorriti MA, et al. Functional interactions between endogenous cannabinoid and opioid systems: focus on alcohol, genetics and drug-addicted behaviors. Curr Drug Targets. 2010;11:406–428.
21. Wills KL, DeVuono MV, Limebeer CL, et al. $CB_1$ receptor antagonism in the bed nucleus of the stria terminalis interferes with affective opioid withdrawal in rats. Behav Neurosci. 2017;131:304–311.
22. Parolaro D, Rubino T, Viganò D, et al. Cellular mechanisms underlying the interaction between cannabinoid and opioid system. Curr Drug Targets. 2010;11:393–405.
23. Wilson-Poe AR, Morgan MM, Aicher SA, et al. Distribution of CB1 cannabinoid receptors and their relationship with mu-opioid receptors in the rat periaqueductal gray. Neuroscience. 2012;213:191–200.
24. Ahmad T, Lauzon NM, de Jaeger X, et al. Cannabinoid transmission in the prelimbic cortex bidirectionally controls opiate reward and aversion signaling through dissociable kappa versus $\mu$-opiate receptor dependent mechanisms. J Neurosci. 2013;33:15642–15651.
25. Braida D, Iosuè S, Pegorini S, et al. Δ9-Tetrahydrocannabinol-induced conditioned place preference and intracerebroventricular self-administration in rats. Eur J Pharmacol. 2004;506:63–69.
26. Singh ME, Verty AN, McGregor IS, et al. A cannabinoid receptor antagonist attenuates conditioned place preference but not behavioural sensitization to morphine. Brain Res. 2004;1026:244–253.
27. Wills KL, Parker LA. Effect of pharmacological modulation of the endocannabinoid system on opiate withdrawal: a review of the preclinical animal literature. Front Pharmacol. 2016;7:187.
28. Yamaguchi T, Hagiwara Y, Tanaka H, et al. Endogenous cannabinoid, 2-arachidonoylglycerol, attenuates naloxone-precipitated withdrawal signs in morphine-dependent mice. Brain Res. 2001;909:121–126.
29. Sagheddu C, Muntoni AL, Pistis M, et al. Endocannabinoid signaling in motivation, reward, and addiction: influences on mesocorticolimbic dopamine function. Int Rev Neurobiol. 2015;125:257–302.
30. Befort K. Interactions of the opioid and cannabinoid systems in reward: insights from knockout studies. Front Pharmacol. 2015;6:6.
31. Martin M, Ledent C, Parmentier M, et al. Cocaine, but not morphine, induces conditioned place preference and sensitization to locomotor responses in CB1 knockout mice. Eur J Neurosci. 2000;12:4038–4046.
32. Rice OV, Gordon N, Gifford AN. Conditioned place preference to morphine in cannabinoid CB1 receptor knockout mice. Brain Res. 2002;945:135–138.
33. Lichtman AH, Sheikh SM, Loh HH, et al. Opioid and cannabinoid modulation of precipitated withdrawal in Δ9-tetrahydrocannabinol and morphine-dependent mice. J Pharmacol Exp Ther. 2001;298:1007–1014.
34. Valverde O, Noble F, Beslot F, et al. Δ9-tetrahydrocannabinol releases and facilitates the effects of endogenous enkephalins: reduction in morphine withdrawal syndrome without change in rewarding effect. Eur J Neurosci. 2001;13:1816–1824.
35. Massaly N, Morón JA, Al-Hasani R. A trigger for opioid misuse: chronic pain and stress dysregulate the mesolimbic pathway and kappa opioid system. Front Neurosci. 2016;10:480.
36. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. National Academies Press: Washington, DC, 2017.
37. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain. 2016;17:739–744.
38. Gruber SA, Sagar KA, Dahlgren MK, et al. Splendor in the grass? A pilot study assessing the impact of medical marijuana on executive function. Front Pharmacol. 2016;7:355.
39. Haroutounian S, Ratz Y, Ginosar Y, et al. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain. 2016;32:1036–1043.
40. Kral AH, Wenger L, Novak SP, et al. Is cannabis use associated with less opioid use among people who inject drugs? Drug Alcohol Depend. 2015;153:236–241.
41. Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. Cannabis Cannabinoid Res. 2017;2:160–166.
42. Bellnier T, Brown GW, Ortega TR. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. Ment Health Clin. 2018;8:110–115.

43. Stith SS, Vigil JM, Adams IM, et al. Effects of legal access to cannabis on scheduled II-V drug prescriptions. J Am Med Dir Assoc. 2018;19:59–64.e1.
44. Cichewicz DL, McCarthy EA. Antinociceptive synergy between Δ9-tetrahydrocannabinol and opioids after oral administration. J Pharmacol Exp Ther. 2003;304:1010–1015.
45. Kazantzis NP, Casey SL, Seow PW, et al. Opioid and cannabinoid synergy in a mouse neuropathic pain model. Br J Pharmacol. 2016;173:2521–2531.
46. Phillips TJ, Cherry CL, Cox S, et al. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One. 2010;5:e14433.
47. Roberts JD, Gennings C, Shih M. Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. Eur J Pharmacol. 2006;530:54–58.
48. Abrams DI, Couey P, Shade SB, et al. Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther. 2011;90:844–851.
49. Wilson AR, Maher L, Morgan MM. Repeated cannabinoid injections into the rat periaqueductal gray enhance subsequent morphine antinociception. Neuropharmacology. 2008;55:1219–1225.
50. Smith PA, Selley DE, Sim-Selley LJ, et al. Low dose combination of morphine and delta9-tetrahydrocannabinol circumvents antinociceptive tolerance and apparent desensitization of receptors. Eur J Pharmacol. 2007;571:129–137.
51. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: a survey of authorized medical cannabis patients. Int J Drug Policy. 2017;42:30–35.
52. Reiman A. Cannabis as a substitute for alcohol and other drugs. Harm Reduc J. 2009;6:35.
53. Finn DP, Jhaveri MD, Beckett SR, et al. Effects of direct periaqueductal grey administration of a cannabinoid receptor agonist on nociceptive and aversive responses in rats. Neuropharmacology. 2003;45:594–604.
54. Jensen TS, Yaksh TL. Comparison of antinociceptive action of morphine in the periaqueductal gray, medial and paramedial medulla in rat. Brain Res. 1986;363:99–113.
55. Varvel SA, Bridgen DT, Tao Q, et al. Delta9-tetrahydrocannbinol accounts for the antinociceptive, hypothermic, and cataleptic effects of marijuana in mice. J Pharmacol Exp Ther. 2005;314:329–337.
56. Cooper ZD, Bedi G, Ramesh D, et al. Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. Neuropsychopharmacology. 2018. [Epub ahead of print]; DOI: 10.1038/s41386-018-0011-2.
57. Li JX, McMahon LR, Gerak LR, et al. Interactions between delta (9)-tetrahydrocannabinol and mu opioid receptor agonists in rhesus monkeys: discrimination and antinociception. Psychopharmacology (Berl). 2008;199:199–208.
58. Christie MJ, Connor M, Vaughan CW, et al. Cellular actions of opioids and other analgesics: implications for synergism in pain relief. Clin Exp Pharmacol Physiol. 2000;27:520–523.
59. Fields HL, Heinricher MM. Anatomy and physiology of a nociceptive modulatory system. Philos Trans R Soc Lond B Biol Sci. 1985;308:361–374.
60. Fyfe LW, Cleary DR, Macey TA, et al. Tolerance to the antinociceptive effect of morphine in the absence of short-term presynaptic desensitization in rat periaqueductal gray neurons. J Pharmacol Exp Ther. 2010;335:674–680.
61. Heinricher MM, Ingram SL. The Brainstem and Nociceptive Modulation. In: Bushnell MC, Basbaum AI, eds. The Senses: A Comprehensive Reference 5.41. Academic Press: Cambridge MA, 2008, pp. 593–626.
62. Wilson-Poe AR, Mitchell VA, Vaughan CW. Postsynaptic mGluR mediated excitation of neurons in midbrain periaqueductal grey. Neuropharmacology. 2013;66:348–354.
63. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9:358–367.
64. Rehni AK, Jaggi AS, Singh N. Opioid withdrawal syndrome: emerging concepts and novel therapeutic targets. CNS Neurol Disord Drug Targets. 2013;12:112–125.
65. Calabria B, Degenhardt L, Briegleb C, et al. Systematic review of prospective studies investigating "remission" from amphetamine, cannabis, cocaine or opioid dependence. Addict Behav. 2010;35:741–749.
66. Ramsey SE, Rounsaville D, Hoskinson R, et al. The need for psychosocial interventions to facilitate the transition to extended-release naltrexone (XR-NTX) treatment for opioid dependence: a concise review of the literature. Subst Abuse. 2016;10:65–68.
67. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. J Addict Dis. 2012;31:207–225.
68. Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs. Substance Abuse and Mental Health Services Administration: Rockville, MD, 2005.
69. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harv Rev Psychiatry. 2015;23:63–75.
70. Fullerton CA, Kim M, Thomas CP, et al. Medication-assisted treatment with methadone: assessing the evidence. Psychiatr Serv. 2014;65:146–157.
71. Gorodetzky CW, Walsh SL, Martin PR, et al. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. Drug Alcohol Depend. 2017;176:79–88.
72. Schuckit MA. Treatment of opioid-use disorders. N Engl J Med. 2016;375:357–368.
73. Novick DM, Salsitz EA, Joseph H, et al. Methadone medical maintenance: an early 21st-century perspective. J Addict Dis. 2015;34:226–237.
74. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technol Assess. 2007;11:1–171, iii–iv.
75. Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. JAMA. 1973;223:665–668.
76. Reed K, Day E, Keen J, et al. Pharmacological treatments for drug misuse and dependence. Expert Opin Pharmacother. 2015;16:325–333.
77. Kimber J, Larney S, Hickman M, et al. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. Lancet Psychiatry. 2015;2:901–908.
78. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med. 2003;348:1786–1795.
79. Services USDOHaH. Substance Abuse and Mental Health Services Administration Detoxification and substance abuse treatment. 2017, p. 49. Available at: https://store.samhsa.gov/shin/content/SMA15-4131/SMA15-4131.pdf (accessed March 18, 2018).
80. Stein BD, Pacula RL, Gordon AJ, et al. Where is buprenorphine dispensed to treat opioid use disorders? The role of private offices, opioid treatment programs, and substance abuse treatment facilities in urban and rural counties. Milbank Q. 2015;93:561–583.
81. Fisher GL, Roget NA. Encyclopedia of substance abuse prevention, treatment, and recovery. Sage: Thousand Oaks, CA, 2009.
82. Rosen K, Gutierrez A, Haller D, et al. Sublingual buprenorphine for chronic pain: a survey of clinician prescribing practices. Clin J Pain. 2014;30:295–300.
83. Jones JD, Manubay JM, Mogali S, et al. Abuse liability of intravenous buprenorphine vs. buprenorphine/naloxone: importance of absolute naloxone amount. Drug Alcohol Depend. 2017;179:362–369.
84. Alho H, Sinclair D, Vuori E, et al. Abuse liability of buprenorphine–naloxone tablets in untreated IV drug users. Drug Alcohol Depend. 2007;88:75–78.
85. Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). J Psychoact Drugs. 2003;35:253–259.
86. Urnoski E. Why is buprenorphine coformulated with naloxone? JAAPA. 2017;30:44–45.
87. Wiegand TJ, Le Lait MC, Bartelson BB, et al. Analysis of the abuse and diversion of the buprenorphine transdermal delivery system. J Pain. 2016;17:745–752.
88. Rosenblatt RA, Andrilla CHA, Catlin M, et al. Geographic and specialty distribution of US physicians trained to treat opioid use disorder. Ann Fam Med. 2015;13:23–26.
89. Sansone RA, Sansone LA. Buprenorphine treatment for narcotic addiction: not without risks. Innov Clin Neurosci. 2015;12:32–36.
90. Dick AW, Pacula RL, Gordon AJ, et al. Growth in buprenorphine waivers for physicians increased potential access to opioid agonist treatment, 2002–11. Health Aff (Millwood). 2015;34:1028–1034.
91. Hutchinson E, Catlin M, Andrilla CHA, et al. Barriers to primary care physicians prescribing buprenorphine. Ann Fam Med. 2014;12:128–133.
92. Kakko J, Svanborg KD, Kreek MJ, et al. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003;361:662–668.

93. Hser YI, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109:79–87.
94. Copenhaver MM, Bruce RD, Altice FL. Behavioral counseling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: a review of the empirical evidence. Am J Drug Alcohol Abuse. 2007;33:643–654.
95. Montoya ID, Schroeder JR, Preston KL, et al. Influence of psychotherapy attendance on buprenorphine treatment outcome. J Subst Abuse Treat. 2005;28:247–254.
96. FDA Requirement. Post market drug safety information for patients and providers. Available at: www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandpro (accessed January 10, 2017).
97. BupPractice. Physician requirements to prescribe buprenorphine. Clinical Tools, Inc. 2014; Available at: https://www.buppractice.com/node/4335 (accessed May 3, 2018).
98. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database Syst Rev. 2017;5:CD002021.
99. Guo S, Manning V, Yang Y, et al. Lofexidine versus diazepam for the treatment of opioid withdrawal syndrome: a double-blind randomized clinical trial in Singapore. J Subst Abuse Treat. 2018;91:1–11.
100. Law FD, Diaper AM, Melichar JK, et al. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: a randomised controlled trial of low dose short-term opiate-dependent individuals. J Psychopharmacol. 2017;31:1046–1055.
101. Deikel SM, Carder B. Attentuation of precipitated abstinence in methadone-dependent rats by delta9-THC. Psychopharmacol Commun. 1976;2:61–65.
102. Fattore L, Deiana S, Spano SM, et al. Endocannabinoid system and opioid addiction: behavioural aspects. Pharmacol Biochem Behav. 2005;81:343–359.
103. Hine B, Torrelio M, Gershon S. Attenuation of precipitated abstinence in methadone-dependent rats by delta 9-THC. Psychopharmacol Commun. 1975;1:275–283.
104. Epstein DH, Preston KL. No evidence for reduction of opioid-withdrawal symptoms by cannabis smoking during a methadone dose taper. Am J Addict. 2015;24:323–328.
105. Navarro M, Carrera MR, Fratta W, et al. Functional interaction between opioid and cannabinoid receptors in drug self-administration. J Neurosci. 2001;21:5344–5350.
106. de Carvalho CR, Takahashi RN. Cannabidiol disrupts the reconsolidation of contextual drug-associated memories in Wistar rats. Addict Biol. 2017;22:742–751.
107. Izzo AA, Borrelli F, Capasso R, et al. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30:515–527.
108. Thomas A, Baillie GL, Phillips AM, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol. 2007;150:613–623.
109. Campos AC, Guimarães FS. Evidence for a potential role for TRPV1 receptors in the dorsolateral periaqueductal gray in the attenuation of the anxiolytic effects of cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:1517–1521.
110. Espejo-Porras F, Fernández-Ruiz J, Pertwee RG, et al. Motor effects of the non-psychotropic phytocannabinoid cannabidiol that are mediated by 5-HT1A receptors. Neuropharmacology. 2013;75:155–163.
111. Seeman P. Cannabidiol is a partial agonist at dopamine D2 high receptors, predicting its antipsychotic clinical dose. Transl Psychiatry. 2016;6:e920.
112. Tham M, Yilmaz O, Alaverdashvili M, et al. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. Br J Pharmacol. 2018.
113. Bisaga A, Sullivan MA, Glass A, et al. The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. Drug Alcohol Depend. 2015;154:38–45.
114. Heikman PK, Muhonen LH, Ojanperä IA. Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine. BMC Psychiatry. 2017;17:245.
115. Bidwell LC, Mueller R, YorkWilliams SL, et al. A novel observational method for assessing acute responses to cannabis: preliminary validation using legal market strains. Cannabis Cannabinoid Res. 2018;3:35–44.
116. Jicha CJ, Lofwall MR, Nuzzo PA, et al. Safety of oral dronabinol during opioid withdrawal in humans. Drug Alcohol Depend. 2015;157:179–183.
117. Lofwall MR, Babalonis S, Nuzzo PA, et al. Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. Drug Alcohol Depend. 2016;164:143–150.
118. Manini AF, Yiannoulos G, Bergamaschi MM, et al. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. J Addict Med. 2015;9:204–210.
119. Mayet A, Lions C, Roux P, et al. Variations in cannabis use level and correlates in opiate-users on methadone maintenance treatment: a French prospective study. J Subst Abuse Treat. 2015;58:100–105.
120. Naef M, Curatolo M, Petersen-Felix S, et al. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain. 2003;105:79–88.
121. Johnson JR, Lossignol D, Burnell-Nugent M, et al. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manag. 2013;46:207–218.
122. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12–19.
123. Cooper ZD, Comer SD, Haney M. Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers. Neuropsychopharmacology. 2013;38:1984–1992.
124. Budney AJ, Hughes JR. The cannabis withdrawal syndrome. Curr Opin Psychiatry. 2006;19:233–238.
125. Budney AJ, Hughes JR, Moore BA, et al. Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry. 2004;161:1967–1977.
126. Budney AJ, Moore BA, Vandrey RG, et al. The time course and significance of cannabis withdrawal. J Abnorm Psychol. 2003;112:393–402.
127. Levin KH, Copersino ML, Heishman SJ, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. Drug Alcohol Depend. 2010;111:120–127.
128. Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. Addiction. 2002;97:621–632.
129. Allsop DJ, Copeland J, Norberg MM, et al. Quantifying the clinical significance of cannabis withdrawal. PLoS One. 2012;7:e44864.
130. Solinas M, Panlilio LV, Antoniou K, et al. The cannabinoid CB1 antagonist N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (SR-141716A) differentially alters the reinforcing effects of heroin under continuous reinforcement, fixed ratio, and progressive ratio schedules of drug self-administration in rats. J Pharmacol Exp Ther. 2003;306:93–102.
131. Fattore L, Spano M, Melis V, et al. Differential effect of opioid and cannabinoid receptor blockade on heroin-seeking reinstatement and cannabinoid substitution in heroin-abstinent rats. Br J Pharmacol. 2011;163:1550–1562.
132. Lazary J, Juhasz G, Hunyady L, et al. Personalized medicine can pave the way for the safe use of CB1 receptor antagonists. Trends Pharmacol Sci. 2011;32:270–280.
133. Thomas KH, Martin RM, Potokar J, et al. Reporting of drug induced depression and fatal and non-fatal suicidal behaviour in the UK from 1998 to 2011. BMC Pharmacol Toxicol. 2014;15:54.
134. Yang P, Wang L, Xie XQ. Latest advances in novel cannabinoid CB2 ligands for drug abuse and their therapeutic potential. Future Med Chem. 2012;4:187–204.
135. Sam AH, Salem V, Ghatei MA. Rimonabant: from RIO to ban. J Obes. 2011;2011:432607.
136. Degenhardt L, Lintzeris N, Campbell G, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend. 2015;147:144–150.
137. Olfson M, Wall MM, Liu SM, et al. Cannabis use and risk of prescription opioid use disorder in the United States. Am J Psychiatry. 2018;175:47–53.

138. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Health. 2018;3:e341–e350.
139. Katsidoni V, Anagnostou I, Panagis G. Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus. Addict Biol. 2013;18:286–296.
140. Budzyńska B, Kruk M, Biała G. Effects of the cannabinoid CB1 receptor antagonist AM 251 on the reinstatement of nicotine-conditioned place preference by drug priming in rats. Pharmacol Rep. 2009;61:304–310.
141. Markos JR, Harris HM, Gul W, et al. Effects of cannabidiol on morphine conditioned place preference in mice. Planta Med. 2018;84:221–224.
142. Hurd YL, Yoon M, Manini AF, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. Neurotherapeutics. 2015;12:807–815.
143. Ren Y, Whittard J, Higuera-Matas A, et al. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J Neurosci. 2009;29:14764–14769.
144. Raby WN, Carpenter KM, Rothenberg J, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. Am J Addict. 2009;18:301–308.
145. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. Drug Alcohol Depend. 2017;173:144–150.
146. Bachhuber MA, Saloner B, Cunningham CO, et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. JAMA Intern Med. 2014;174:1668–1673.
147. National Institute on Drug Abuse. Opioid overdoses by state drugabuse.gov. National Institutes of Health, 2018; Available at: https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state/california-opioid-summary (accessed May 3, 2018).
148. Kim JH, Santaella-Tenorio J, Mauro C, et al. State medical marijuana laws and the prevalence of opioids detected among fatally injured drivers. Am J Public Health. 2016;106:2032–2037.
149. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare Part D. Health Aff (Millwood). 2016;35:1230–1236.
150. Bradford AC, Bradford WD, Abraham A, et al. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. JAMA Intern Med. 2018;178:667–672.
151. Birnbaum HG, White AG, Reynolds JL, et al. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. Clinical J Pain 2006;22:667–676.
152. Bradford AC, Bradford WD. Factors driving the diffusion of medical marijuana legalisation in the United States. Drugs Educ Prev Policy. 2017;24:75–84.
153. Hasin DS. US Epidemiology of cannabis use and associated problems. Neuropsychopharmacology. 2018;43:195–212.
154. Wen H, Hockenberry JM. Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. JAMA Intern Med. 2018;178:673–679.
155. Liang D, Bao Y, Wallace M, et al. Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993–2014. Addiction. 2018. [Epub ahead of print]; DOI: 10.1111/add.14382.
156. Robson P. Human studies of cannabinoids and medicinal cannabis. Handb Exp Pharmacol. 2005:719–756.
157. Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. J Affect Disord. 2018;235:198–205.
158. Smart R, Caulkins JP, Kilmer B, et al. Variation in cannabis potency and prices in a newly-legal market: evidence from 30 million cannabis sales in Washington State. Addiction. 2017;112:2167–2177.
159. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol. 1994;2:244–268.
160. Yamamoto T, Takada K. Current perspective—role of cannabinoid receptor in the brain as it relates to drug reward. Jpn J Pharmacol. 2001;84:229–236.
161. Haney M, Ramesh D, Glass A, et al. Naltrexone maintenance decreases cannabis self-administration and subjective effects in daily cannabis smokers. Neuropsychopharmacology. 2015;40:2489–2498.
162. Curran HV, Freeman TP, Mokrysz C, et al. Keep off the grass? Cannabis, cognition and addiction. Nat Rev Neurosci. 2016;17:293–306.
163. Ranganathan M, Carbuto M, Braley G, et al. Naltrexone does not attenuate the effects of intravenous Δ9-tetrahydrocannabinol in healthy humans. Int J Neuropsychopharmacol. 2012;15:1251–1264.
164. Clasen MM, Flax SM, Hempel BJ, et al. Antagonism of the kappa opioid receptor attenuates THC-induced place aversions in adult male Sprague-Dawley rats. Pharmacol Biochem Behav. 2017;163:30–35.
165. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. J Addict Med. 2014;8:153–163.
166. Maher DP, Carr DB, Hill K, et al. Cannabis for the treatment of chronic pain in the era of an opioid epidemic: a symposium-based review of sociomedical science. Pain Med. 2017 [Epub ahead of print]; doi: 10.1093/pm/pnx143.
167. Department of Health. Medical marijuana program. Department of Health: State of New Jersey, 2018.
168. National Conference of State Legislatures. State medical marijuana laws. 2018. Available at: http://ncsl.org (accessed March 18, 2018).
169. Fitzcharles MA, Eisenberg E. Medical cannabis: a forward vision for the clinician. Eur J Pain. 2018;22:485–491.
170. Evanoff AB, Quan T, Dufault C, et al. Physicians-in-training are not prepared to prescribe medical marijuana. Drug Alcohol Depend. 2017;180:151–155.

**Cite this article as:** 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.

## Abbreviations Used

BNST = bed nucleus of stria terminalis
CB1 = cannabinoid 1
CBD = cannabidiol
CeA = central amygdala
CPA = Conditioned Place Aversion
CPP = conditioned place preference
CUD = cannabis use disorder
DSM = *Diagnostic and Statistical Manual of Mental Disorders*
FARS = Fatality Analysis Reporting System
KO = knockout
KOR = kappa opioid receptor
MOR = mu opioid receptor
NIDA = National Institute of Drug Abuse
OUD = opioid use disorder
PFC = prefrontal cortex
POAs = prescription opioid analgesics
THC = tetrahydrocannabinol
VTA = ventral tegmental area

# REFERENCE #14

Cochrane Library

Cochrane Database of Systematic Reviews

# Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Review)

Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S

Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S.
Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy.
*Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD009464.
DOI: 10.1002/14651858.CD009464.pub2.

**www.cochranelibrary.com**




WILEY

## TABLE OF CONTENTS

[Intervention Review]

# Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Lesley A Smith[1], Fredric Azariah[2], Verna TC Lavender[3], Nicola S Stoner[4], Silvana Bettiol[5]

[1]Department of Psychology, Social Work and Public Health, Oxford Brookes University, Oxford, UK. [2]School of Health and Social Care, Oxford Brookes University, Oxford, UK. [3]Department of Clinical Health Care, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK. [4]Pharmacy, Oxford University Hospitals NHS Trust, Oxford, UK. [5]Department of Medicine and Paramedicine, Faculty of Health, University of Tasmania, Hobart, Australia

Contact address: Lesley A Smith, Department of Psychology, Social Work and Public Health, Oxford Brookes University, Jack Straws Lane, Marston, Oxford, OX3 0FL, UK. lesleysmith@brookes.ac.uk.

**Editorial group:** Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
**Publication status and date:** New, published in Issue 11, 2015.

**Citation:** Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD009464. DOI: 10.1002/14651858.CD009464.pub2.



## ABSTRACT

### Background

Cannabis has a long history of medicinal use. Cannabis-based medications (cannabinoids) are based on its active element, delta-9-tetrahydrocannabinol (THC), and have been approved for medical purposes. Cannabinoids may be a useful therapeutic option for people with chemotherapy-induced nausea and vomiting that respond poorly to commonly used anti-emetic agents (anti-sickness drugs). However, unpleasant adverse effects may limit their widespread use.

### Objectives

To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer.

### Search methods

We identified studies by searching the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO and LILACS from inception to January 2015. We also searched reference lists of reviews and included studies. We did not restrict the search by language of publication.

### Selection criteria

We included randomised controlled trials (RCTs) that compared a cannabis-based medication with either placebo or with a conventional anti-emetic in adults receiving chemotherapy.

### Data collection and analysis

At least two review authors independently conducted eligibility and risk of bias assessment, and extracted data. We grouped studies based on control groups for meta-analyses conducted using random effects. We expressed efficacy and tolerability outcomes as risk ratio (RR) with 95% confidence intervals (CI).

**Main results**

We included 23 RCTs. Most were of cross-over design, on adults undergoing a variety of chemotherapeutic regimens ranging from moderate to high emetic potential for a variety of cancers. The majority of the studies were at risk of bias due to either lack of allocation concealment or attrition. Trials were conducted between 1975 and 1991. No trials involved comparison with newer anti-emetic drugs such as ondansetron.

**Comparison with placebo**

People had more chance of reporting complete absence of vomiting (3 trials; 168 participants; RR 5.7; 95% CI 2.6 to 12.6; low quality evidence) and complete absence of nausea and vomiting (3 trials; 288 participants; RR 2.9; 95% CI 1.8 to 4.7; moderate quality evidence) when they received cannabinoids compared with placebo. The percentage of variability in effect estimates that was due to heterogeneity rather than chance was not important ($I^2$ = 0% in both analyses).

People had more chance of withdrawing due to an adverse event (2 trials; 276 participants; RR 6.9; 95% CI 1.96 to 24; $I^2$ = 0%; very low quality evidence) and less chance of withdrawing due to lack of efficacy when they received cannabinoids, compared with placebo (1 trial; 228 participants; RR 0.05; 95% CI 0.0 to 0.89; low quality evidence). In addition, people had more chance of 'feeling high' when they received cannabinoids compared with placebo (3 trials; 137 participants; RR 31; 95% CI 6.4 to 152; $I^2$ = 0%).

People reported a preference for cannabinoids rather than placebo (2 trials; 256 participants; RR 4.8; 95% CI 1.7 to 13; low quality evidence).

**Comparison with other anti-emetics**

There was no evidence of a difference between cannabinoids and prochlorperazine in the proportion of participants reporting no nausea (5 trials; 258 participants; RR 1.5; 95% CI 0.67 to 3.2; $I^2$ = 63%; low quality evidence), no vomiting (4 trials; 209 participants; RR 1.11; 95% CI 0.86 to 1.44; $I^2$ = 0%; moderate quality evidence), or complete absence of nausea and vomiting (4 trials; 414 participants; RR 2.0; 95% CI 0.74 to 5.4; $I^2$ = 60%; low quality evidence). Sensitivity analysis where the two parallel group trials were pooled after removal of the five cross-over trials showed no difference (RR 1.1; 95% CI 0.70 to 1.7) with no heterogeneity ($I^2$ = 0%).

People had more chance of withdrawing due to an adverse event (5 trials; 664 participants; RR 3.9; 95% CI 1.3 to 12; $I^2$ = 17%; low quality evidence), due to lack of efficacy (1 trial; 42 participants; RR 3.5; 95% CI 1.4 to 8.9; very low quality evidence) and for any reason (1 trial; 42 participants; RR 3.5; 95% CI 1.4 to 8.9; low quality evidence) when they received cannabinoids compared with prochlorperazine.

People had more chance of reporting dizziness (7 trials; 675 participants; RR 2.4; 95% CI 1.8 to 3.1; $I^2$ = 12%), dysphoria (3 trials; 192 participants; RR 7.2; 95% CI 1.3 to 39; $I^2$ = 0%), euphoria (2 trials; 280 participants; RR 18; 95% CI 2.4 to 133; $I^2$ = 0%), 'feeling high' (4 trials; 389 participants; RR 6.2; 95% CI 3.5 to 11; $I^2$ = 0%) and sedation (8 trials; 947 participants; RR 1.4; 95% CI 1.2 to 1.8; $I^2$ = 31%), with significantly more participants reporting the incidence of these adverse events with cannabinoids compared with prochlorperazine.

People reported a preference for cannabinoids rather than prochlorperazine (7 trials; 695 participants; RR 3.3; 95% CI 2.2 to 4.8; $I^2$ = 51%; low quality evidence).

In comparisons with metoclopramide, domperidone and chlorpromazine, there was weaker evidence, based on fewer trials and participants, for higher incidence of dizziness with cannabinoids.

Two trials with 141 participants compared an anti-emetic drug alone with a cannabinoid added to the anti-emetic drug. There was no evidence of differences between groups; however, the majority of the analyses were based on one small trial with few events.

**Quality of the evidence**

The trials were generally at low to moderate risk of bias in terms of how they were designed and do not reflect current chemotherapy and anti-emetic treatment regimens. Furthermore, the quality of evidence arising from meta-analyses was graded as low for the majority of the outcomes analysed, indicating that we are not very confident in our ability to say how well the medications worked. Further research is likely to have an important impact on the results.

**Authors' conclusions**

Cannabis-based medications may be useful for treating refractory chemotherapy-induced nausea and vomiting. However, methodological limitations of the trials limit our conclusions and further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions.

## PLAIN LANGUAGE SUMMARY

### Cannabis-based medicine for nausea and vomiting in people treated with chemotherapy for cancer

#### Background

As many as three-quarters of people who receive chemotherapy experience nausea (feeling sick) and vomiting (being sick), which many find distressing. While conventional anti-sickness medicines are effective, they do not work for everyone, all of the time. Therapeutic drugs based on the active ingredient of cannabis, known as THC (delta-9-tetrahydrocannabinol), have been approved for use as anti-sickness medicines in some countries.

#### Review question

This review evaluated how well cannabis-based medicines work for treating nausea and vomiting due to chemotherapy treatment in people with cancer, and what the side effects were.

#### Main findings

This review of 23 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) found that fewer people who received cannabis-based medicines experienced nausea and vomiting than people who received placebo (a pretend medicine). The proportion of people who experienced nausea and vomiting who received cannabis-based medicines was similar to conventional anti-nausea medicines. However, more people experienced side effects such as 'feeling high', dizziness, sedation (feeling relaxed or sleepy) and dysphoria (feeling uneasy or dissatisfied) and left the study due to the side effects with cannabis-based medicines, compared with either placebo or other anti-nausea medicines. In trials where people received cannabis-based medicines and conventional medicines in turn, overall people preferred the cannabis-based medicines.

#### Quality of the evidence

The trials were of generally of low to moderate quality and reflected chemotherapy treatments and anti-sickness medicines that were around in the 1980s and 1990s. Also, the results from combining studies on the whole were of low quality. This means that we are not very confident in our ability to say how well the anti-sickness medicines worked, and further research reflecting modern treatment approaches is likely to have an important impact on the results.

Cannabis-based medicines may be useful for treating chemotherapy-induced nausea and vomiting that responds poorly to commonly used anti-sickness medicines.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

**Cannabinoids compared with placebo for chemotherapy-induced nausea and vomiting**

**Patient or population:** people with chemotherapy-induced nausea and vomiting
**Intervention:** cannabinoids
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Cannabinoids | | | | |
| **Absence of nausea** (follow-up) | 3 per 100 | 6 per 100 (1 to 63) | **RR 2.0** (0.2 to 21) | 96 (2) | ⊕⊕◯◯ **low**[3,5] | RR **>** 1 indicates treatment favours cannabinoids |
| **Absence of vomiting** (follow-up) | 6 per 100 | 34 per 100 (16 to 76) | **RR 5.7** (2.6 to 12.6) | 168 (3) | ⊕⊕◯◯ **low**[3,5] | RR **>** 1 indicates treatment favours cannabinoids |
| **Absence of nausea and vomiting** (follow-up) | 11 per 100 | 32 per 100 (20 to 52) | **RR 2.9** (1.8 to 4.7) | 288 (3) | ⊕⊕⊕◯ **moderate**[3] | RR **>** 1 indicates treatment favours cannabinoids |
| **Participant preference** (follow-up) | Low-risk value[2] | | **RR 4.8** (1.7 to 13) | 256 (2) | ⊕⊕◯◯ **low**[3,4] | RR **>** 1 indicates treatment favours cannabinoids |
| | 8 per 100 | 38 per 100 (14 to 104) | | | | |
| | High-risk value[2] | | | | | |
| | 22 per 100 | 106 (37 to 286) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Withdrawal any reason** (follow-up) | 10 per 1000 | 3 per 1000 (0.1 to 7) | **RR 0.31** (0.01 to 7) | 33 (1) | ⊕◯◯◯ **very low**[1,3,5] | RR **< 1** indicates treatment favours cannabinoids |
| **Withdrawal due to adverse event** (follow-up) | 80 per 1000 | 4 per 1000 (0.0 to 72) | **RR 6.9** (1.96 to 24) | 276 (2) | ⊕◯◯◯ **very low**[1,3,5] | RR **< 1** indicates treatment favours cannabinoids |

*The **assumed risk** for all outcomes is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Sparse data.
[2] The low- and high-risk values are the two extreme proportions of people with a preference for one drug over another.
[3] Limitations in the design (cross-over study) and high attrition.
[4] Unexplained heterogeneity.
[5] Imprecision.

# BACKGROUND

## Description of the condition

Nausea and vomiting are considered the most stressful adverse effects of chemotherapy by people with cancer (Barowski 1984; de Boer-Dennert 1997; Russo 2014). Up to 75% of all people with cancer experience chemotherapy-related nausea and vomiting (Schwartzberg 2007), which can lead to depression, anxiety and a feeling of helplessness, lower quality of life and may affect chemotherapy adherence (Dodds 1985; Janelsins 2013; Wilcox 1982).

Guidelines that inform standard protocols and algorithms ensure best practice in managing chemotherapy-induced nausea and vomiting (Basch 2011; NCCN 2014; Roila 2010). However, standardised care and clinical decision-making occurs within the context of individualised care, where focus on a person's preference is key to reducing chemotherapy-related stress in people with cancer. People's preference for cancer treatment is illustrated by several studies that report people's preferences for specific chemotherapy regimens based on quality of life (reduced treatment toxicity), rather than treatment efficacy (increased predicted survival) (Beusterien 2014; Dubey 2005; Kuchuk 2013; Sun 2002). Therefore, it is important to consider use of all approved anti-emetics that treat chemotherapy-induced nausea and vomiting, where people may have a preference for one or another type of treatment.

During the 1990s, serotonin (5-HT3) receptor antagonists, combined with dexamethasone, became the gold standard in the prevention of vomiting caused by chemotherapy (Gralla 1999; MASCC 1998). Episodes of chemotherapy-induced nausea and vomiting are classified by distinct clinical phases: acute - within the first 24 hours of treatment; delayed - following the first 24 hours of treatment and anticipatory - a learned response where refractory nausea and vomiting have been experienced during previous chemotherapy cycles, which results in nausea and vomiting prior to a subsequent treatment cycle (Roila 2010). Nowadays, the anti-emetics indicated for chemotherapy with high emesis-inducing potential are 5-HT3 receptor antagonists, dexamethasone and aprepitant given during the acute emetic phase (Basch 2011; Gralla 2013; NCCN 2014; Olver 2004). However, if there is failure to respond, or there is an increase in vomiting, this cannot be corrected by increasing the dose or frequency of administration of the prophylactic anti-emetics (5-HT3 receptor antagonists, dexamethasone and aprepitant). People who experience refractory nausea and vomiting (i.e. people who do not respond to first-line prophylactic anti-emetics) can have additional anti-emetics added to their existing prophylactic anti-emetic regimen, such as a dopamine antagonist (metoclopramide, domperidone), a phenothiazine (prochlorperazine or levomepromazine), an antihistamine (cyclizine) or a butyrophenone (haloperidol) anti-emetic (Gralla 1999; Gralla 2013). Benzodiazepines (lorazepam) can also be added to the prophylactic anti-emetic regimen for refractory people, particularly those who are anxious or experience anticipatory nausea and vomiting (Gralla 1999). Dexamethasone is one of the most effective anti-emetics for delayed nausea and vomiting, so people experiencing delayed refractory emesis can be prescribed an extended course of dexamethasone on a reducing dosage (Gralla 1999; Huang 2004; Ioannidis 2000). More recently, there have been reports of olanzapine being an effective adjunctive treatment for refractory nausea and vomiting (Gralla 2013). A second-generation 5HT3 receptor antagonist, palonosetron, is effective in refractory nausea and vomiting to substitute for a first-generation 5HT3 receptor antagonist (Gralla 2013). In addition, if people are unable to tolerate oral 5HT3 receptor antagonists, other formulations can be considered such as a 24-hour granisetron transdermal patch, an orally disintegrating ondansetron melt, or ondansetron oral film (Gralla 2013). Consideration should also be made for other formulations of adjunctive anti-emetics, such as buccal or rectal formulations (Gralla 2013).

According to Walsh 2003, cannabinoids, the active agents derived from cannabis (marijuana), may be considered for controlling nausea and vomiting as fourth-line agents. They have been recommended in international anti-emetic guidelines for the prevention of chemotherapy-induced nausea and vomiting (Gralla 1999). Cannabinoids are thought to work through different mechanisms to other agents given for nausea and vomiting (see: How the intervention might work) and may be effective in people with cancer who respond poorly to commonly used agents (Machado Rocha 2008).

## Description of the intervention

Cannabis has been used for medicinal purposes throughout history (Karniol 2001). It was listed on the American pharmacopoeia until 1944 (Bonnie 1974), when it was removed due to political pressure and was banned in the USA (Walsh 2003). Although cannabis has not been re-listed on the American pharmacopoeia, in 1986 the Food and Drug Administration (FDA) authorised the use of its active element, delta-9-tetrahydrocannabinol (delta-9-THC), for medical purposes (Walsh 2003), to treat the adverse effects of nausea and vomiting in people with cancer receiving chemotherapy (Gralla 1999).

Currently, there are two synthetic delta-9-THC (cannabinoid) agents that have been evaluated in clinical trials that are approved for the treatment of nausea and vomiting in people with cancer treated with chemotherapy. These are oral formulations of trans(+)-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo(b,d),pyran-9-one, nabilone, and l(6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol, dronabinol.

## How the intervention might work

Cannabinoids affect the user by interacting with various receptors in different areas of the brain (Grotenhermen 2002). To date, two types of cannabinoid receptors have been identified, termed CB1 and CB2. Two substances naturally occurring in the brain that bind to and activate CB1 receptors are anandamide (Devane 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam 1995; Sugiura 1995). The cannabinoid receptors, and other naturally occurring substances that bind to them, are collectively termed the 'endocannabinoid system' (Rodríguez de Fonseca 2005). The blockage of CB1 cannabinoid receptors induces vomiting, suggesting the existence of cannabinoid receptors within the areas of the brain related to nausea and vomiting. This also suggests that the delta-9-THC anti-emetic activity may be due to stimulation of the CB1 receptor (Darmani 2001).

### Why it is important to do this review

A systematic review of randomised controlled trials (RCTs) published up to the year 2000 concluded that cannabinoids may be useful for controlling chemotherapy-induced nausea and vomiting, but that harmful adverse effects may limit their widespread use (Tramer 2001). This meta-analysis pooled placebo-controlled and active controlled trials together. Furthermore, a more recently published systematic review came to a similar conclusion regarding effectiveness, but did not report on the adverse effects (Machado Rocha 2008). Cannabinoids are currently rarely used in clinical practice, and the publication of a systematic review of cannabinoids in highly emetic chemotherapy will provide an evidence base for their use in people with refractory nausea and vomiting.

## OBJECTIVES

To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

RCTs of cross-over or parallel group design with active or placebo control groups, or both.

#### Types of participants

Adults aged 18 years and over presenting with any type of cancer and receiving chemotherapeutic treatment, independent of gender and clinical setting. The chemotherapeutic regimens include drugs with low, moderate or high emetic potential.

We excluded children and young people aged under 18 years, since prevention and treatment of chemotherapy-induced nausea and vomiting, including use of cannabinoids, has been reported in this population in another Cochrane Review (Phillips 2010).

For the purpose of this review, chemotherapeutic treatments were those containing cytotoxic systemic anti-cancer treatments.

Two review authors (VL and NS) independently classified chemotherapeutic regimens, containing one or more chemotherapy agents as low, moderate, moderate to high, or high emetic potential using both American Society of Clinical Oncology (ASCO) guidelines (Basch 2011) and MASCC (Multinational Association of Supportive Care in Cancer)/European Society for Medical Oncology (ESMO) guidelines (Roila 2010). We resolved differences in assessment by discussion.

#### Types of interventions

Experimental arm: licensed pharmacological interventions based on cannabinoids derived from cannabis: nabilone and dronabinol used either as monotherapy or adjunct to conventional dopamine antagonists.

Control arm: placebo or conventional dopamine antagonists.

#### Types of outcome measures

##### Primary outcomes

- Complete control of nausea and vomiting (absence of episodes of nausea and vomiting without use of rescue medication) in the acute phase (within 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours' treatment with chemotherapy) of nausea and vomiting.
- Complete control of vomiting (absence of episodes of vomiting without use of rescue medication) in the acute and delayed phases of nausea and vomiting.
- Complete control of nausea (absence of episodes of nausea without use of rescue medication) in the acute and delayed phases of nausea and vomiting.

##### Secondary outcomes

- Withdrawal due to adverse effects of anti-emetic.
- Withdrawal due to any anti-emetic-related reason.
- Withdrawal due to lack of anti-emetic efficacy.
- Cross-over studies only: participant preference for one or other of the interventions (cannabis or control).
- Incidence of particular adverse effects: 'feeling high', sedation, euphoria, dizziness, heightened sense of anxiety or

agitation (dysphoria), depression, hallucinations, paranoia, hypotension, focal dystonia, extrapyramidal effects and oculogyric crisis.

## Search methods for identification of studies

We sought papers in all languages and carried out translations wherever necessary.

### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2015, Issue 1), MEDLINE accessed via Ovid (from 1966 to January week 3 2015), EMBASE accessed via Ovid (from 1980 to January week 3 2015), PsycINFO accessed via Ovid (from inception to January week 2 2015) and LILACS (from inception to January 2015). Appendix 1, Appendix 2, Appendix 3, Appendix 4, and Appendix 5 show the search strategies.

All relevant articles were identified on PubMed and, using the 'related articles' feature, we carried out a further search for newly published articles.

### Searching other resources

#### Unpublished and grey literature

We searched metaRegister (www.controlled-trials.com/rct), Physicians Data Query (www.nci.nih.gov), wwwclinicaltrials.gov, and www.cancer.gov/clinicaltrials for ongoing trials. We searched for conference proceedings and abstracts through ZETOC ( zetoc.mimas.ac.uk) and WorldCat Dissertations.

#### Handsearching

We examined bibliographical references of all the relevant studies in detail in order to find studies not identified in the electronic search, and handsearched key textbooks and previous systematic reviews and reports of conferences (i.e. ESMO and ASCO).

## Data collection and analysis

### Selection of studies

We downloaded all the titles and abstracts retrieved by electronic searching to a reference management database; we removed duplicates and three review authors (LS, FA, SB) independently examined the remaining references. We excluded those studies that clearly did not meet the inclusion criteria and we obtained copies of the full text of potentially relevant references. Three review authors (LS, FA, SB) independently assessed the eligibility of the retrieved papers. The review authors were not blinded to the authors' names, institutions and journals of publication. We resolved disagreements by discussion and documented the reasons for exclusion in the Characteristics of excluded studies table.

### Data extraction and management

For the included studies, two review authors (FA, LS) independently abstracted data on characteristics of study participants (inclusion criteria, age, gender, type of cancer and stage of disease, comorbidities, co-interventions and chemotherapy regimens); dose, frequency, route of administration and duration of experimental and control interventions; risk of bias (see Assessment of risk of bias in included studies); outcomes (see Types of outcome measures) and deviations from the protocol onto a data abstraction form specially designed for the review and checked by a third author (SB). We resolved disagreements by discussion or by appeal.

For dichotomous outcomes (such as number of people with chemotherapy-induced nausea and vomiting per treatment group that did not present with symptoms of nausea and vomiting, described as absence of episodes of nausea and vomiting, to the end of the period of study; or withdrawals), we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed in order to estimate a risk ratio (RR).

Wherever possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned. For cross-over studies, we extracted information on the number of cross-over periods, duration of washout periods and whether a paired design had been taken into consideration in the analysis.

We notes the time points at which outcomes were collected and reported.

#### Unit of analysis

For cross-over studies, we extracted the number of events as the numerator and the number analysed as the denominator for each treatment period.

### Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using the Cochrane's 'Risk of bias' tool (Higgins 2011). This included assessment of:

- method used for generating the randomisation sequence allocation of participants to the treatment arms;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- reporting of incomplete outcome data (studies were considered at high risk of bias if more than 80% of people were assessed for primary outcomes): proportion of losses to follow-up and association with treatment arms, reasons for drop-out and association of drop-outs with treatment arms;

- selective reporting of outcomes;
- any other sources of bias that were pre-defined as carry-over effects and unbiased data available for analysis for cross-over trials.

Three review authors independently applied the 'Risk of bias' tool and resolved differences by discussion. We summarised results in both a 'Risk of bias' graph and a 'Risk of bias' summary. We interpreted results of meta-analyses in light of the findings with respect to risk of bias.

### Measures of treatment effect

For dichotomous outcomes, we calculated the RR and its respective 95% confidence interval (CI). We incorporated cross-over trials in the meta-analyses using reported summary effect estimates. Where the carry-over effects were evident for a particular study, then we only used the data for the first period for the meta-analysis.

### Dealing with missing data

We did not impute missing outcome data for any of the outcomes. If contact details could be obtained, we contacted trial authors and requested missing data.

### Assessment of heterogeneity

We assessed the heterogeneity between the trials by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). We interpreted the $I^2$ value according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* as follows (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Where there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

### Assessment of reporting biases

We examined funnel plots corresponding to meta-analysis of the primary outcome if there were at least 10 trials included in the meta-analysis to assess the potential for small-study effects such as publication bias.

### Data synthesis

Where we judged the trials sufficiently similar, we pooled their results in a meta-analysis. For dichotomous outcomes, we combined the RR for each study. We used random-effects models with inverse variance weighting for all meta-analyses due to the clinical and methodological diversity of the studies (see Characteristics of included studies table).

If trials had multiple treatment groups, we divided the 'shared' comparison group into the number of treatment groups and treated comparisons between each treatment group and the split comparison group as independent comparisons.

### Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses for the primary outcome if sufficient trials were available:

- history of cannabis use, naive users versus prior users of cannabis;
- history of exposure to chemotherapy, chemotherapy naive versus prior chemotherapy treatment;
- type of cannabinoid agent, nabilone versus dronabinol.

### Sensitivity analysis

We carried out sensitivity analyses for the primary outcome, if sufficient trials were available, excluding trials at high risk of bias and trials of a cross-over design. We also analysed the influence of the following factors on estimates of treatment effect:

- repeating the analysis excluding trials where chemotherapeutic regimens had low or low-moderate emetic potential, or the emetic potential was unclassifiable;
- repeating the analysis excluding trials where the primary outcome data were gathered after more than 24 hours of chemotherapeutic treatment.

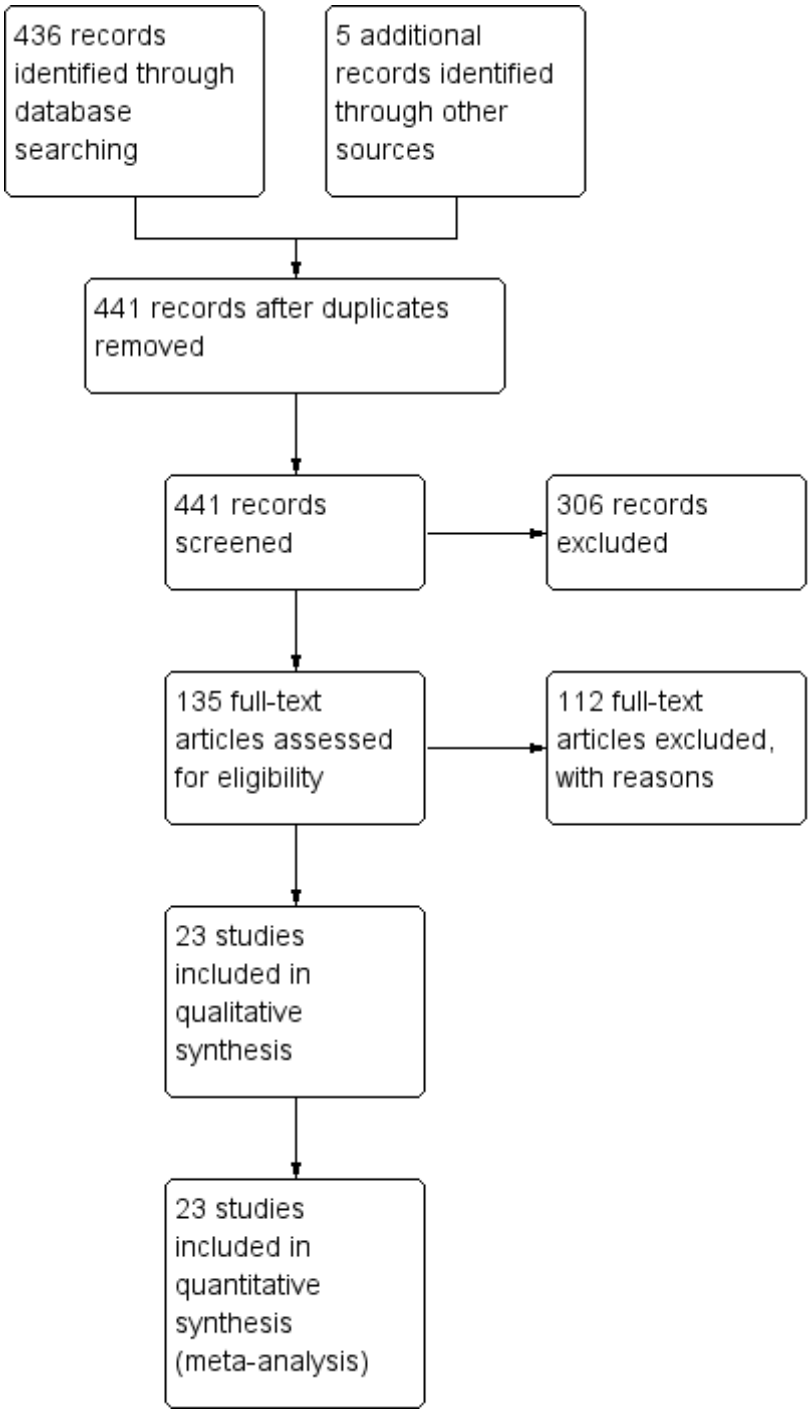
## RESULTS

### Description of studies

#### Results of the search

The search identified 441 records of which 135 were potentially eligible. We obtained hard copies of the full article of these articles for further consideration and excluded 112 (Figure 1). We identified no unpublished data.

**Figure 1. Identification and selection of randomised controlled trials for review inclusion.**



## Included studies

Of the 23 included RCTs, the majority (19) were of cross-over design with four that were of parallel group design (Frytak 1979; Gralla 1984; Lane 1991; Pomeroy 1986).

The RCTs included people with a variety of cancers undergoing different chemotherapy regimens ranging from moderate to high anti-emetic potential, except for one of low emetic potential (Chang 1979a); five were unclassifiable as reporting of chemotherapy regimen was unclear (Kleinman 1983; Lane 1991; Levitt 1982; Sallan 1975a; Ungerleider 1982). Four trials were conducted on participants who were cannabis naive (Ahmedzai 1983; Frytak 1979; Johansson 1982; Lane 1991), one where 88% of participants were naive (Chang 1981), and one where 27% of participants were naive (Chang 1979a). One study excluded current users of cannabis (McCabe 1988), and in the other trials previous exposure to cannabinoids was unclear.

Nine RCTs compared cannabinoids given as monotherapy compared with placebo (Chang 1979a; Chang 1981; Frytak 1979; Jones 1982; Kluin-Neleman 1979; Levitt 1982; McCabe 1988; Sallan 1975a; Wada 1982), with another anti-emetic agent (prochlorperazine) in 11 RCTs (Ahmedzai 1983; Einhorn 1981; Frytak 1979; Herman 1979; Johansson 1982; Lane 1991; McCabe 1988; Niiranen 1985; Orr 1981; Steele 1980; Ungerleider 1982), metoclopramide in two RCTs (Crawford 1986; Gralla 1984), domperidone in one RCT (Pomeroy 1986), and chlorpromazine in one RCT (George 1983). Cannabinoids were also given as co-therapy with another anti-emetic agent compared with an anti-emetic agent alone in two RCTs (Kleinman 1983; Lane 1991).

Two different cannabis-based medications were tested: nabilone in 12 RCTs (Ahmedzai 1983; Crawford 1986; Einhorn 1981; George 1983; Herman 1979; Johansson 1982; Jones 1982; Levitt 1982; Niiranen 1985; Pomeroy 1986; Steele 1980; Wada 1982), and dronabinol in 11 RCTs (Chang 1979a; Chang 1981; Frytak 1979; Gralla 1984; Kleinman 1983; Kluin-Neleman 1979; Lane 1991; McCabe 1988; Orr 1981; Sallan 1975a; Ungerleider 1982).

Dosing schedules varied across trials. Nabilone when given as monotherapy was administered most commonly as a fixed dose of 2 mg twice daily with lower doses administered when given as co-therapy. Dronabinol was mainly given at doses according to body surface area and ranged from 10 mg/$m^2$ twice daily to 15 mg/$m^2$ six times daily. Both were given as an oral formulations. In two trials, oral dronabinol was replaced with cannabis-based cigarettes if the participants vomited (Chang 1979a; Chang 1981).

The majority of the nausea or vomiting (or both) outcomes were reported for those that occurred within a 24-hour period. However, for some trials, it was unclear when outcomes were assessed and they may have been reported for a longer time-period (Herman 1979; Johansson 1982; Jones 1982; Kluin-Neleman 1979; Lane 1991; Levitt 1982). Trials were conducted between 1975 and 1991.

## Excluded studies

We excluded 112 studies for reasons described in the Characteristics of excluded studies table. The main reasons were due to not being a primary study (i.e. a review, editorial or letter) (64) or were a non-randomised single-arm study (eight). RCTs were excluded due to not being an eligible treatment group (six); comparison (six) or a relevant outcome (one); recruited children (three); only presenting preliminary (three) or subsidiary results (one); having no extractable data (eight) or a duplicate of an existing study (10). Two were unobtainable.

## Risk of bias in included studies

The trials were of variable quality ranging from low to moderate (Figure 2; Figure 3).

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.**

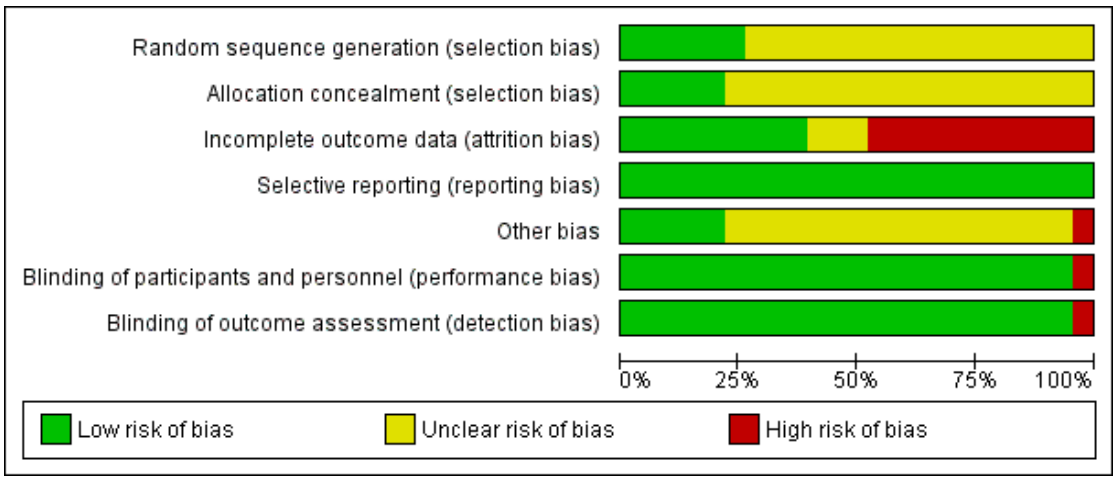
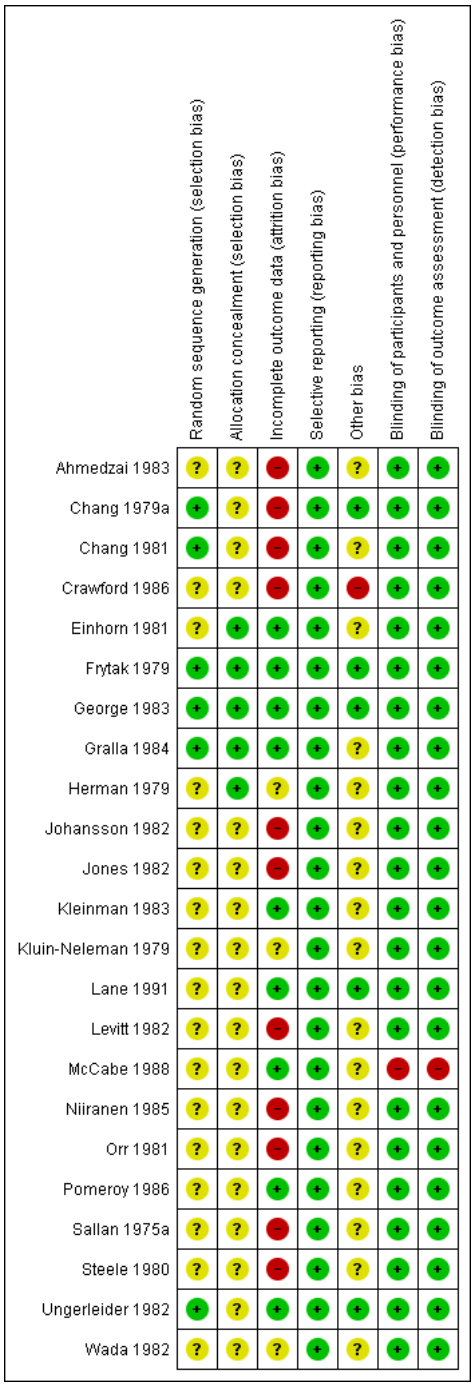


**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.**



### Allocation

Six trials adequately reported how the randomisation sequence was generated (Chang 1979a; Chang 1981; Frytak 1979; George 1983; Gralla 1984; Ungerleider 1982); the remaining 17 trials were unclear. Concealment of allocation was adequate in five trials (Einhorn 1981; Frytak 1979; George 1983; Gralla 1984; Herman 1979), and unclear in the remaining 18 trials.

### Blinding

The majority of the trials were described as double-blind, which was implemented by using identical tablets. Eight were reported as double-blind, but it was unclear how this was achieved (Crawford 1986; Johansson 1982; Jones 1982; Lane 1991; Levitt 1982; Steele 1980; Ungerleider 1982; Wada 1982), and one study made no attempt at blinding (McCabe 1988).

### Incomplete outcome data

Most trials were prone to attrition bias with only 9/23 trials judged as low risk of bias.

### Selective reporting

All of the trials reported on the incidence of nausea or vomiting (or both); however, not all contributed to the meta-analyses. We were unable to include data for trials if they only reported results for nausea and vomiting as mean frequency of episodes, rather than the proportion of participants with and without nausea or vomiting (or both). While a reduction in severity of nausea or a reduction in vomiting episodes (or both) may be considered a worthwhile outcome for people with chemotherapy-induced nausea and vomiting, in these included trials, nausea severity was not measured with a validated instrument and episodes of vomiting were not analysed using standard methods for such (count) data. Therefore, we have not reported these data.

### Other potential sources of bias

A large proportion of the trials were of cross-over design. We a*ssumed that the washout period was sufficient* and there were no carry-over effects of treatment due to the gap between chemotherapy treatment cycles, which would typically be around three weeks. The main potential source of bias was due to lack of information reported on whether a paired analysis was performed or not, and it was unclear if the groups were balanced at baseline.

## Effects of interventions

See: **Summary of findings for the main comparison** Cannabinoids compared with placebo for chemotherapy-induced nausea and vomiting; **Summary of findings 2** Cannabinoids compared with other anti-emetic agent for chemotherapy-induced nausea and vomiting; **Summary of findings 3** Cannabinoid plus other anti-emetic agent compared with other anti-emetic monotherapy for chemotherapy-induced nausea and vomiting

### Cannabinoids versus placebo

Nine trials with 819 participants compared cannabinoids with placebo (Chang 1979a; Chang 1981; Frytak 1979; Jones 1982; Kluin-Neleman 1979; Levitt 1982; Orr 1981; Sallan 1975a; Wada 1982), although not all trials contributed data for each outcome.

#### Primary outcome - anti-emetic efficacy

Two trials involving 96 participants showed no evidence of a difference between groups in the proportion of participants reporting complete absence of nausea with cannabinoids compared with placebo (RR 2.0; 95% CI 0.19 to 21; Analysis 1.1).

Three trials involving 168 participants showed that people had more chance of reporting complete absence of vomiting when they received cannabinoids compared with when they received placebo (RR 5.7; 95% CI 2.6 to 13). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was not important ($I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.33; Analysis 1.2).

Three trials involving 288 participants showed that people had more chance of reporting complete absence of nausea and vomiting when they received cannabinoids compared with placebo (RR 2.9; 95% CI 1.8 to 4.7). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was not important ($I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.50; Analysis 1.3).

Subgroup analyses, comparing results in trials with cannabis-naive people to trials where participants either had previous experience with cannabis or where previous use was unclear, showed no evidence of a difference between the two subgroups (P value = 0.4) with respect to absence of nausea and vomiting.

#### Secondary outcome - participant preference

Two trials involving 256 participants showed that people had more chance of reporting a preference for cannabinoids compared with placebo (RR 4.8; 95% CI 1.7 to 13) with substantial heterogeneity ($I^2$ = 71%, $Tau^2$ = 0.43, $Chi^2$ test for heterogeneity P value = 0.06; Analysis 1.9).

#### Secondary outcomes - tolerability and adverse events

One trial involving 33 participants showed no evidence of a difference between groups in the proportion of participants withdrawing for any reason (RR 0.31; 95% CI 0.01 to 7.21; Analysis 1.10). Participants had more chance of withdrawing due to an adverse event when they received cannabinoids compared with placebo (2 trials; 226 participants; RR 6.9; 95% CI 2.0 to 24; Analysis 1.11), and less chance of withdrawing due to lack of efficacy (1 trial; 228 participants; RR 0.05; 95% CI 0.0 to 0.89; Analysis 1.12).

Participants had more chance of reporting 'feeling high' (3 trials; 137 participants; RR 31; 95% CI 6.4 to 152). The percentage of the variability in effect estimates that is due to heterogeneity rather than chance was not important ($I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.95; Analysis 1.6).

There was no evidence of a difference between groups in the proportion of participants reporting depression (1 trial; 16 participants; RR 3.8; 95% CI 0.18 to 80; Analysis 1.4), dysphoria (2 trials; 96 participants; RR 9.0; 95% CI 0.50 to 161; Analysis 1.5), paranoia (1 trial; 64 participants; RR 3.0; 95% CI 0.13 to 71; Analysis 1.7), or sedation (2 trials; 139 participants; RR 4.5; 95% CI 0.35 to 58; Analysis 1.8) with substantial heterogeneity ($I^2$ = 72%, $Tau^2$ = 2.65, $Chi^2$ test for heterogeneity P value = 0.06).

The CIs for the estimates shown above are wide reflecting the uncertainty of these estimates.

### Cannabinoids versus prochlorperazine

Nine trials with 1221 participants compared cannabinoids with prochlorperazine (Ahmedzai 1983; Frytak 1979; Herman 1979; Johansson 1982; Lane 1991; McCabe 1988; Niiranen 1985; Steele 1980; Ungerleider 1982), although not all trials contributed data for each outcome.

#### Primary outcome - anti-emetic efficacy

Five trials involving 258 participants showed no evidence of a difference between groups in the proportion of participants reporting no nausea (RR 1.5; 95% CI 0.67 to 3.2) with substantial heterogeneity ($I^2$ = 58%, $Tau^2$ = 0.33, $Chi^2$ test for heterogeneity P value = 0.05; Analysis 2.1).

Four trials involving 209 participants showed no evidence of a difference between groups in the proportion of participants reporting no vomiting (RR 1.1; 95% CI 0.86 to 1.4). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was not important ($I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.53; Analysis 2.3).

Four trials involving 414 participants showed no evidence of a difference between groups in the proportion of participants reporting absence of nausea and vomiting (RR 2.0; 95% CI 0.74 to 5.4) with substantial heterogeneity ($I^2$ = 60%, $Tau^2$ = 0.51, $Chi^2$ test for heterogeneity P value = 0.06; Analysis 2.5). Sensitivity analysis, where the two parallel group trials were pooled after removal of the five cross-over trials, had an RR of 1.1 (95% CI 0.70 to 1.7) with no heterogeneity($I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.56).

Subgroup analyses - comparing results in trials with cannabis-naive people to trials where participants either had previous experience with cannabis or where previous use was unclear, showed no evidence of a difference between the two subgroups with respect to absence of nausea (P value = 0.11), but a difference between the subgroups for absence of nausea and vomiting with a smaller effect in people with no previous cannabis use (P value = 0.007). We were unable to conduct a subgroup analysis for absence of vomiting as all trials were of people who were cannabis naive (Analysis 2.6).

In addition, there was no evidence of a difference between subgroups comprised of different cannabinoid medications for absence of nausea (P value = 0.54), absence of vomiting (P value = 0.60) or absence of nausea and vomiting (P value = 0.10). The subgroup analyses did not explain the source of heterogeneity. There were insufficient data to perform other subgroup analyses listed in methods of analysis.

#### Secondary outcome - participant preference

Seven trials involving 695 participants showed participants had more chance of reporting a preference for cannabinoids compared with prochlorperazine (RR 3.2; 95% CI 2.2 to 4.7) with substantial heterogeneity ($I^2$ = 53%, $Tau^2$ = 0.13, $Chi^2$ test for heterogeneity P value = 0.05; Analysis 2.17).

#### Secondary outcomes - tolerability and adverse events

Based on one trial with 42 participants, participants had more chance of withdrawing for any reason (RR 3.5; 95% CI 1.4 to 8.9; Analysis 2.18), and due to lack of anti-emetic efficacy (RR 3.5; 95% CI 1.4 to 8.9; Analysis 2.20) when they received cannabinoids compared with prochlorperazine.

Five trials with 664 participants showed participants had more chance of withdrawing due to an adverse event when they received cannabinoids compared with prochlorperazine (RR 3.9; 95% CI 1.3 to 12) with unimportant heterogeneity($I^2$ = 17%, $Tau^2$ = 0.31, $Chi^2$ test for heterogeneity P value = 0.31; Analysis 2.19).

Participants had more chance of reporting the following adverse events when they received cannabinoids compared with prochlorperazine: dizziness (7 trials; 675 participants; RR 2.4; 95% CI 1.8 to 3.1; unimportant heterogeneity: $I^2$ = 12%, $Tau^2$ = 0.02, $Chi^2$ test for heterogeneity P value = 0.34; Analysis 2.8), dysphoria (3 trials; 192 participants; RR 7.2; 95% CI 1.3 to 39; unimportant heterogeneity: $I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.75; Analysis 2.9), euphoria (2 trials; 280 participants; RR 18; 95% CI 2.4 to 133; unimportant heterogeneity: $I^2$ = 0%, $Tau^2$ = 0.00, $Chi^2$ test for heterogeneity P value = 0.47; Analysis 2.10), 'feeling high' (4 trials; 389 participants; RR 6.2; 95% CI 3.5 to 11; unimportant heterogeneity: $I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$

test for heterogeneity P value = 0.75; Analysis 2.11), and sedation (8 trials; 947 participants; RR 1.4; 95% CI 1.2 to 1.8; moderate heterogeneity: $I^2$ = 31%, $Tau^2$ = 0.02, $Chi^2$ test for heterogeneity P value = 0.18; Analysis 2.15).

There was no evidence of a difference between groups in the proportion of participants reporting depression (3 trials; 317 participants; RR 0.81; 95% CI 0.51 to 1.3; unimportant heterogeneity: $I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.47; Analysis 2.16), hallucinations (2 trials; 144 participants; RR 5.4; 95% CI 0.66 to 44; unimportant heterogeneity: $I^2$ = 0%, $Tau^2$ = 0.0, $Chi^2$ test for heterogeneity P value = 0.80; Analysis 2.12), postural hypotension (3 trials; 305 participants; RR 1.2; 95% CI 0.52 to 2.9; moderate heterogeneity: $I^2$ = 41%, $Tau^2$ = 0.29, $Chi^2$ test for heterogeneity P value = 0.18; Analysis 2.13), or paranoia (1 trial; 42 participants; RR 3.0; 95% CI 0.13 to 70; Analysis 2.14).

### Cannabinoid versus metoclopramide

Two trials with 57 participants compared cannabinoid with metoclopramide (Crawford 1986; Gralla 1984), although both trials did not contribute data for each outcome.

#### Primary outcome - anti-emetic efficacy

Neither trial reported data for the proportion of participants with absence of nausea or vomiting (or both) (Crawford 1986; Gralla 1984).

#### Secondary outcome - participant preference

One trial involving 64 participants showed no evidence of a difference between groups in the proportion of participants reporting a preference for cannabinoids (RR 1.2; 95% CI 0.61 to 2.4; Analysis 2.17).

#### Secondary outcomes - tolerability and adverse events

Neither trial reported withdrawals.

Participants had more chance of reporting dizziness (1 trial, 30 participants; RR 12; 95% CI 1.8 to 81; Analysis 2.8), and postural hypotension (1 trial, 30 participants; RR 17; 95% CI 1.1 to 270; Analysis 2.13) when they received cannabinoids compared with metoclopramide. The CIs for these estimates were very wide reflecting the uncertainty of these estimates.

There was no evidence of a difference between groups in the proportion of participants reporting 'feeling high' (1 trial, 30 participants; RR 3.0; 95% CI 0.35 to 26; Analysis 2.11), or sedation (1 trial; 30 participants; RR 0.93; 95% CI 0.73 to 1.2; Analysis 2.15).The CIs for these estimates were very wide reflecting the uncertainty of these estimates. There were no dystonic reactions in either treatment group.

### Cannabinoids versus domperidone

One trial with 38 participants compared cannabinoids versus domperidone (Pomeroy 1986).

#### Primary outcome - anti-emetic efficacy

The trial did not report data for the proportion of participants with absence of nausea or vomiting (or both).

#### Secondary outcome - participant preference

The trial did not report data for participant preference.

#### Secondary outcomes - tolerability and adverse events

There was no evidence of a difference between groups in the proportion of participants withdrawing due to lack of efficacy (RR 0.14; 95% CI 0.01 to 2.7; Analysis 2.20) or withdrawal due to an adverse event (RR 0.14; 95% CI 0.01 to 2.7; Analysis 1.11), with both estimates based on very low event rates.

Participants had more chance of reporting dizziness when they received cannabinoids compared with domperidone (RR 2.8; 95% CI 1.1 to 7.1; Analysis 2.8).

There was no evidence of a difference between groups in the proportion of participants reporting euphoria (RR 5.0; 95% CI 0.26 to 98; Analysis 2.10), postural hypotension (RR 4.0; 95% CI 0.49 to 33; Analysis 2.13) or sedation (RR 1.2; 95% CI 0.66 to 2.3; Analysis 2.15).

### Cannabinoids versus chlorpromazine

One trial with 20 participants compared cannabinoids with chlorpromazine (George 1983).

#### Primary outcome - anti-emetic efficacy

The trial did not report data for anti-emetic efficacy.

#### Secondary outcome - participant preference

There was no evidence of a difference between groups in participants' preferences for treatment with cannabinoids or chlorpromazine (RR 2.0; 95% CI 0.83 to 4.8; Analysis 2.17).

#### Secondary outcomes - tolerability and adverse events

The trial did not report data for withdrawals.

There was no evidence of a difference between groups in the proportion of participants reporting euphoria (RR 3.0; 95% CI 0.13 to 70; Analysis 2.10), postural hypotension (RR 7.0; 95% CI 0.95 to 52; Analysis 2.13), or sedation (RR 1.7; 95% CI 0.85 to 3.4; Analysis 2.15), with few events giving rise to wide CIs around the point estimates.

### Cannabinoid plus other anti-emetic agent versus other anti-emetic agent monotherapy

Two trials with 105 participants compared cannabinoid plus other anti-emetic agent with other anti-emetic agent monotherapy ( Kleinman 1983; Lane 1991), although neither trial contributed data for all outcomes. The majority of the analyses were based on one small trial with few events (Lane 1991).

#### Primary outcome - anti-emetic efficacy

There was no evidence of a difference between groups in the proportion of participants reporting no nausea (RR 11; 95% CI 0.61 to 182; Analysis 3.1).
There was no evidence of a difference between groups in the proportion of participants reporting no vomiting (RR 1.5; 95% CI 0.69 to 3.1; Analysis 3.2).
There was no evidence of a difference between groups in the proportion of participants reporting no nausea or vomiting (RR 1.6; 95% CI 0.68 to 3.6; Analysis 3.3).

#### Secondary outcome - participant preference

The trials did not report data for participant preference.

#### Secondary outcomes - tolerability and adverse events

There was no evidence of a difference between groups in the proportion of participants withdrawing due to any reason (RR 1.3; 95% CI 0.41 to 4.2; Analysis 3.9).
There was no evidence of a difference between groups in the proportion of participants withdrawing due to an adverse event (RR 7.0; 95% CI 0.88 to 55; Analysis 3.10).
There was no evidence of a difference between groups in the proportion of participants withdrawing due to lack of efficacy (RR 0.12; 95% CI 0.01 to 2.0; Analysis 3.11).
There was no evidence of a difference between groups in the proportion of participants reporting depression (no participants in either group; Analysis 3.4), dizziness (RR 2.1; 95% CI 0.21 to 21; Analysis 3.5), dysphoria (RR 7.3; 95% CI 0.40 to 134; Analysis 3.6), paranoia (RR 5.2; 95% CI 0.27 to 103; Analysis 3.7), or sedation (RR 1.8; 95% CI 0.48 to 6.4; Analysis 3.8).

## ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

**Cannabinoids compared with other anti-emetic agent for chemotherapy-induced nausea and vomiting**

**Patient or population:** people with chemotherapy-induced nausea and vomiting
**Intervention:** cannabinoids
**Comparison:** other anti-emetic agent

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Other anti-emetic agent | Cannabinoids | | | | |
| **Absence of nausea** (follow-up) | 37 per 100 | 56 per 100 (25 to 118) | **RR 1.46** (0.67 to 3.15) | 258 (5) | ⊕⊕◯◯ **low**[3,4] | RR **>** **1** indicates treatment favours cannabinoids |
| **Absence of vomiting** (follow-up) | Low-risk value[2] | | **RR 1.1** (0.86 to 1.4) | 209 (4) | ⊕⊕⊕◯ **moderate**[3] | RR **>** **1** indicates treatment favours cannabinoids |
| | 10 per 1 000 | 11 per 1 000 (9 to 14) | | | | |
| | High-risk value[2] | | | | | |
| | 70 per 100 | 77 per 100 (60 to 98) | | | | |
| **Absence of nausea and vomiting** (follow-up) | Low-risk value[2] | | **RR 2.0** (0.74 to 5.4) | 414 (4) | ⊕⊕◯◯ **low**[3,4] | RR **>** **1** indicates treatment favours cannabinoids |
| | 1 per 100 | 2 per 100 (1 to 5) | | | | |
| | High-risk value[2] | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 42 per 100 | 84 per 100 (31 to 227) | | | | |
| **Participant preference** (follow-up) | 23 per 100 | 64 per 100 (44 to 92) | **RR 2.8** (1.9 to 4.0) | 799 (9) | ⊕⊕◯◯ **low**[3,4] | RR **> 1** indicates treatment favours cannabinoids |
| **Withdrawal any reason** (follow-up) | 19 per 100 | 67 per 100 (27 to 171) | **RR 3.5** (1.4 to 9.0) | 42 (1) | ⊕⊕◯◯ **low**[1,3] | RR **< 1** indicates treatment favours cannabinoids |
| **Withdrawal due to lack of efficacy** (follow-up) | 20 per 100 | 19 per 100 (1 to 420) | **RR 0.97** (0.04 to 21) | 118 (2) | ⊕◯◯◯ **very low**[1,3,4] | RR **< 1** indicates treatment favours cannabinoids |
| **Withdrawal due to adverse event** (follow-up) | 3 per 100 | 10 per 100 (4 to 24) | **RR 3.2** (1.3 to 8.0) | 740 (6) | ⊕⊕◯◯ **low**[3,5] | RR **< 1** indicates treatment favours cannabinoids |

*The **assumed risk** for all outcomes is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Sparse data.
[2] The low- and high-risk values are the two extreme proportions of people with a preference for one drug over another.
[3] Limitations in the design (cross-over study) and high attrition.
[4] Unexplained heterogeneity.
[5] Imprecision.

**Cannabinoid plus other anti-emetic agent compared with other anti-emetic monotherapy for chemotherapy-induced nausea and vomiting**

**Patient or population:** people with chemotherapy-induced nausea and vomiting
**Intervention:** cannabinoid plus other anti-emetic agent
**Comparison:** anti-emetic monotherapy

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Anti-emetic monotherapy | Cannabinoid plus other anti-emetic agent | | | | |
| **Absence of nausea** (follow-up) | 1 per 100 | 10 per 100 (0 to 183) | **RR 10** (0.61 to 183) | 37 (1) | ⊕○○○ **very low**[1,2,3] | RR **> 1** indicates treatment favours cannabinoids |
| **Absence of vomiting** (follow-up) | 29 per 100 | 44 per 100 (20 to 90) | **RR 1.5** (0.69 to 3.1) | 89 (2) | ⊕⊕○○ **low**[1,2] | RR **> 1** indicates treatment favours cannabinoids |
| **Absence of nausea and vomiting** (follow-up) | 30 per 100 | 48 per 100 (20 to 108) | **RR 1.6** (0.68 to 3.6) | 37 (1) | ⊕⊕○○ **low**[1,2] | RR **> 1** indicates treatment favours cannabinoids |
| **Withdrawal any reason** (follow-up) | 20 per 100 | 26 per 100 (8 to 84) | **RR 1.3** (0.41 to 4.2) | 41 (1) | ⊕⊕○○ **low**[1,2] | RR **< 1** indicates treatment favours cannabinoids |
| **Withdrawal due to adverse event** (follow-up) | 1 per 100 | 7 per 100 (1 to 55) | **RR 7.0** (0.88 to 55) | 105 (2) | ⊕○○○ **very low**[1,2,3] | RR **< 1** indicates treatment favours cannabinoids |
| **Withdrawal due to lack of efficacy** (follow-up) | 20 per 100 | 2 per 100 (0 to 40) | **RR 0.12** (0.01 to 2.0) | 41 (1) | ⊕⊕○○ **low**[1,2] | RR **< 1** indicates treatment favours cannabinoids |

*The **assumed risk** for all outcomes is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Sparse data.
[2] Limitations in the design (cross-over study) and high attrition.
[3] Imprecision.

# DISCUSSION

## Summary of main results

The included trials showed that cannabinoids were more effective than placebo and were similar to conventional anti-emetics for treating chemotherapy-induced nausea and vomiting. However, despite causing more adverse events than placebo, overall there was weak evidence that people receiving chemotherapy for cancer preferred cannabinoids to placebo with stronger evidence that people preferred them to other anti-emetics.

Cannabinoids were highly effective. When compared with placebo, participants who received cannabinoids were five times as likely to report complete absence of vomiting, and three times as likely to report complete absence of nausea and vomiting. Although, some participants were six times more likely to withdraw from the study due to an adverse event with cannabinoids, other participants were more likely to withdraw due to lack of efficacy with placebo. Adverse events associated with cannabinoids were reported, however, the only one with evidence of a difference between cannabinoids and placebo was 'feeling high'. Overall, there was weak evidence that participants preferred cannabinoids to placebo.

When cannabinoids were compared with conventional anti-emetic drugs, there was no evidence of a difference for nausea, vomiting, or nausea and vomiting. The majority of the data for these analyses were from comparison with prochlorperazine. However, participants were three or four times more likely to withdraw due to an adverse event with cannabinoids than prochlorperazine. Dizziness, dysphoria, 'feeling high' and sedation were all more likely with cannabinoids. Dizziness in particular was more likely with cannabinoids compared with metoclopramide and domperidone. Overall, there was evidence that participants preferred cannabinoids to conventional anti-emetics; however, the majority of the trials were of prochlorperazine.

There may be an additional benefit of administering a cannabinoid with another anti-emetic agent. These benefits include reduced nausea, vomiting, and nausea and vomiting. Adverse events were similar to those for comparisons with anti-emetics given as monotherapy, but there were insufficient data to make firm conclusions.

## Overall completeness and applicability of evidence

The trials included in this review were on adults with a wide variety of cancers undergoing a wide range of chemotherapy regimens. Many of the trials included participants who were refractory to conventional anti-emetic medications. The synthetic cannabis-based compounds were given orally and were either dronabinol or nabilone. The most informative RCTs were the ones that compared a cannabis-based medication with a conventional anti-emetic, rather than placebo. These trials showed that cannabis-based medications had similar anti-emetic effects compared with prochlorperazine and metoclopramide.

Nowadays, people receiving moderate to highly emetogenic chemotherapy regimens will be prescribed combination prophylactic anti-emetic regimens including a 5-$HT_3$ antagonist and steroid, and perhaps also include a neurokinin-1 (NK-1) inhibitor for very highly emetogenic regimens (NCCN 2015). In the event of a person experiencing breakthrough or refractory, acute chemotherapy-induced nausea and vomiting, an additional agent from a different pharmacological class of anti-emetics would be recommended, such as metoclopramide, prochlorperazine or lorazepam (NCCN 2015). Cannabis-based anti-emetics offer an alternative additional anti-emetic agent for breakthrough or refractory acute chemotherapy-induced nausea and vomiting. Since there is a lack of studies that compare the use of cannabinoids to 5-$HT_3$ antagonists and NK-1 inhibitors, this review found no evidence to support the use of cannabinoids in place of current prophylactic combination anti-emetic regimens.

## Quality of the evidence

Overall, the trials were of variable quality (very low to moderate by Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). Strengths included the use of blinding by using double-dummy preparations by the majority of the trials. However, it is possible that the trials were at risk of observer bias, due to the characteristic adverse effect profile of cannabinoids. The risk of bias from selective reporting of the primary outcome was low. The majority of the trials were unclear with respect to methods used to generate randomisation sequence and whether randomisation was concealed, so may be at risk of selection bias. A major weakness lies in the fact that a large proportion of the trials were of cross-over design, and we were unable to adjust the data to take into account the paired data, which will result in narrower CIs around effect estimates. Another weakness was high risk of bias from attrition from the trials. This was largely due to participants being excluded from analyses in the cross-over trials if they did not complete all cross-over periods. The summary of findings are shown in Summary of findings for the main comparison; Summary of findings 2; and Summary of findings 3. The quality of the evidence for most outcomes was generally of low quality. The main reasons were due to risk of bias, imprecise results due to few studies or few events (or both) and unexplained heterogeneity. The impact of the downgrading decisions means that further research is likely to influence the confidence in our estimates of effects and may change the estimates.

## Potential biases in the review process

Some trials only reported episodes of nausea and vomiting, rather than the proportion of participants with no nausea and vomiting, therefore we did not include these results in meta-analyses. We also analysed dichotomous outcomes from the cross-over studies without adjusting the analyses, which potentially gives rise to more precise (narrower CIs) estimates of effect.

In order to avoid publication bias, we searched for ongoing trials in clinical trial registry databases; however, we identified no further trials.

### Agreements and disagreements with other studies or reviews

Our findings are in broad agreement with previously published systematic reviews (Machado Rocha 2008; Tramer 2001). We have updated and extended these earlier reviews by pooling placebo-controlled trials separately from trials with active comparison groups, and where cannabis was given as co-therapy with another anti-emetic, and reporting on tolerability as well as efficacy outcomes.

## AUTHORS' CONCLUSIONS

### Implications for practice

The widespread use of cannabis-based medicines for management of nausea and vomiting with chemotherapy is unlikely due to the adverse effects they cause. However, cannabinoids are a useful adjunctive treatment to consider for people on moderately or highly emetic chemotherapy that are refractory to other anti-emetic treatments, when all other options of therapy have been tried. Consideration needs to be made of the adverse effect profile of the cannabinoids, and how the adverse effects may be exacerbated with other concurrent anti-emetic treatments, as well as the age of the person. This systematic review will be valuable evidence for clinicians and future development of international guidelines to summarise the evidence available.

### Implications for research

Adequate study design is important for anti-emetic studies, ideally using a double-blind trial design that is stratified for known prognostic factors, such as gender, age, alcohol intake, previous experience of chemotherapy, emetic potential of chemotherapy and a person's susceptibility to motion sickness (De Mulder 1992; Olver 1992a; Olver 1992b; Pater 1984). It is preferable for people to be chemotherapy naive and receiving the same chemotherapy regimens, or, if that is not possible, to receive those of the same emetogenicity as classified by international guidelines. Uniform anti-emetic regimens should be used, when comparing an adjunctive anti-emetic being added to the regimen in one arm (Rhodes 1984). Studies that compare the use of newer anti-emetics that have efficacy for treating refractory nausea and vomiting (olanzapine and palonosetron) with cannabinoids would also be informative. It is difficult to compare anti-emetic studies (Martin 1992), due to the variation in anti-emetic doses, routes of administration, time periods of assessment of nausea and vomiting, assessment of episodes of nausea and vomiting, and any additional anti-emetics that may have been administered. It also needs to be clear whether acute or delayed (or both) nausea and vomiting is being assessed, and there is also a variation in the definitions of complete response across studies, which impacts on comparing studies (Pater 1984). In the original anti-emetic trials, assessment of nausea and vomiting has been inconsistent where no reliable and valid measures have been used, which also impacts on their analysis and interpretation (Pater 1984; Rhodes 1984).

While cross-over trials are attractive to evaluate this type of therapy, they are susceptible to loss of participants if not all cross-over to the second and subsequent phases of the trial. Following recommendations of the CONSORT (Consolidated Standards of Reporting Trials) statement for cross-over studies would improve interpretation of such studies.

## ACKNOWLEDGEMENTS

We thank Jo Morrison for clinical and editorial advice on the protocol, Jane Hayes for designing the search strategy and running the searches in all databases for us, Sarah Howcutt for translation of one article from French (George 1983), and Dax Steins for translation of one article from Dutch (Kluin-Nelemans 1981a). Finally, we thank Clare Jess and Gail Quinn for their contribution to the editorial process.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health.

# REFERENCES

## References to studies included in this review


**Ahmedzai 1983** *{published data only}*
Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *British Journal of Cancer* 1983; **48**(5):657–63.

**Chang 1979a** *{published data only}*
Chang AE, Shiling DJ, Stillman RC. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Annals of Internal Medicine* 1979; **91**(6):819–24.

**Chang 1981** *{published data only}*
Chang AE, Shiling DJ, Stillman RC. A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer* 1981;**47**(7):1746–51.

**Crawford 1986** *{published data only}*
Crawford SM, Buckman R. Nabilone and metoclopramide in the treatment of nausea and vomiting due to cisplatinum: a double blind study. *Medical Oncology and Tumor Pharmacotherapy* 1986;**3**(1):39–42.

**Einhorn 1981** *{published data only}*
Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. *Journal of Clinical Pharmacology* 1981;**21**(8-9 Suppl):64S–9S.

**Frytak 1979** *{published data only}*
Frytak S, Moertel CG, O'Fallon JR. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. *Annals of Internal Medicine* 1979;**91**(6): 825–30.

**George 1983** *{published data only}*
George M, Pejovic MH, Thuaire M, Kramar A, Wolff JP. Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin [French]. *Biomedicine & Pharmacotherapy* 1983;**37**(1):24–7.

**Gralla 1984** *{published data only}*
Gralla RJ Tyson LB Bordin LA. Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treatment Reports* 1984;**68** (1):163–72.

**Herman 1979** *{published data only}*
Herman TS, Einhorn LH, Jones SE, Nagy C, Chester AB, Dean JC, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. New England Journal of Medicine 1979; Vol. 300:1295–7.

**Johansson 1982** *{published data only}*
Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. *Cancer Treatment Reviews* 1982;**9**(Suppl B):25–33.

**Jones 1982** *{published data only}*
Jones SE, Durant JR, Greco FA, Robertone A. A multi-institutional phase III study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting. *Cancer Treatment Reviews* 1982;**9**(Suppl B):45–8.

**Kleinman 1983** *{published data only}*
Kleinman S, Weitzman SA, Cassem N, Andrews E. Double blind trial of delta-9-tetrahydrocannabinol (THC) versus placebo as an adjunct to prochlorperazine for chemotherapy-induced vomiting. *Current Therapeutic Research - Clinical and Experimental* 1983;**33**(61):1014–7.

**Kluin-Neleman 1979** *{published data only}*
Kluin-Neleman JC, Neleman FA, Meuwissen OJ, Maes RA. Delta 9-tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancer chemotherapy; a double-blind cross-over trial against placebo. *Veterinary & Human Toxicology* 1979;**21**(5):338–40.

**Lane 1991** *{published data only}*
Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JL, Hamm J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *Journal of Pain and Symptom Management* 1991; **6**(6):352–9.

**Levitt 1982** *{published data only}*
Levitt M. Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. *Cancer Treatment Reviews.* 1982;**9**(Suppl B): 49–53.

**McCabe 1988** *{published data only}*
McCabe M, Smith FP, Macdonald JS, Woolley PV, Goldberg D, Schein PS. Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. *Investigational New Drugs* 1988;**6**(3):243–6.

**Niiranen 1985** *{published data only}*
Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *American Journal of Clinical Oncology: Cancer Clinical Trials* 1985;**8**(4):336–40.

**Orr 1981** *{published data only}*
Orr LE, McKernan JF. Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. *Journal of Clinical Pharmacology* 1981;**21**(8-9 Suppl):76S–80S.

**Pomeroy 1986** *{published data only}*
Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. *Cancer Chemotherapy and Pharmacology* 1986;**17**(3):285–8.

**Sallan 1975a** *{published data only}*
Sallan SE, Zinberg NE, Frei E. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer

chemotherapy. New England Journal of Medicine 1975; Vol. 293:795–7.

**Steele 1980** *{published data only}*
Steele N, Gralla RJ, Braun Jr DW, Young CW. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Cancer Treatment Reports* 1980;**64**(2-3):219–24.

**Ungerleider 1982** *{published data only}*
Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. *Cancer* 1982;**50**(4):636–45.

**Wada 1982** *{published data only}*
Wada JK, Bogdon DL, Gunnell JC. Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. *Cancer Treatment Reviews* 1982;**9**(Suppl B): 39–44.

## References to studies excluded from this review

**Aapro 1981** *{published data only}*
Aapro MS. Prevention of chemotherapy-induced nausea and vomiting in patients with cancer. *Arizona Medicine* 1981;**38**(11):843–5.

**Allan 1987** *{published data only}*
Allan SG. Mechanisms and management of chemotherapy-induced nausea and vomiting. *Blood Reviews* 1987;**1**(1): 50–7.

**Anderson 1981** *{published data only}*
Anderson PO, McGuire GG. Delta-9-tetrahydrocannabinol as an antiemetic. *American Journal of Hospital Pharmacy* 1981;**38**(5):639–46.

**Artim 1983** *{published data only}*
Artim R, Dibella N. [Tetrahydrocannabinol plus prochlorperazine for refractory nausea and vomiting]. Proceedings of the 19th annual meeting of the American Society of Clinical Oncology. 1983; Vol. 2:85.

**Bateman 1982** *{published data only}*
Bateman DN, Rawlins MD. Therapeutic potential of cannabinoids. *British Medical Journal Clinical Research Ed* 1982;**284**(6324):1211–2.

**Ben 2006** *{published data only}*
Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. *Journal of Ethnopharmacology* 2006; **105**(1-2):1–25.

**Biedrzycki 2007** *{published data only}*
Biedrzycki BA. Evolving paradigms in chemotherapy-induced nausea and vomiting and symptom management for the breast cancer patient. *ONS Connect* 2007;**22**(8 suppl):9–10.

**Broder 1982** *{published data only}*
Broder LE, Lean NL, Hilsenbeck SG. A randomized blinded clinical trial comparing delta-9-tetrahydrocannabinol (THC) and hydroxizine (HZ) as antiemetics (AE) for cancer chemotherapy (CT). *Proceedings of the American Association for Cancer Research* 1982;**23**:514.

**Carey 1983** *{published data only}*
Carey MP, Burish TG, Brenner DE. Delta-9-tetrahydrocannabinol in cancer chemotherapy: research problems and issues. *Annals of Internal Medicine* 1983;**99** (1):106–14.

**Chan 1987** *{published data only}*
Chan HSL, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics* 1987;**79**(6):946–52.

**Chang 1979b** *{published data only}*
Chang AE, Shiling DJ, Stillman RC. A prospective randomized trial of delta-9-tetrahydrocannabinol (THC) as an antiemetic in patients receiving high dose methotrexate (MTX). American Society of Clinical Oncology 1979: No–C-357.

**Citron 1985** *{published data only}*
Citron ML Herman TS Vreeland F. Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. *Cancer Treatment Reports* 1985;**69**(1):109–12.

**Cocchetto 1981** *{published data only}*
Cocchetto DM, Cook LF, Cato AE. A critical review of the safety and antiemetic efficacy of delta-9-tetrahydrocannabinol. *Drug Intelligence and Clinical Pharmacy* 1981;**15**(11):867–75.

**Colls 1980a** *{published data only}*
Colls BM. Cannabis and cancer chemotherapy. Lancet 1980; Vol. 1:1187–8.

**Colls 1980b** *{published data only}*
Colls BM, Ferry DG, Gray AJ. The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. *New Zealand Medical Journal* 1980;**91**(662): 449–51.

**Cone 1982** *{published data only}*
Cone LA, Greene DS, Helm NA. Use of nabilone in the treatment of chemotherapy-induced vomiting in an outpatient setting. *Cancer Treatment Reviews* 1982;**9**(Suppl B):63–70.

**Costa 2007** *{published data only}*
Costa B. On the pharmacological properties of 9-tetrahydrocannabinol (THC). *Chemistry and Biodiversity* 2007;**4**(8):1664–77.

**Cotter 2009** *{published data only}*
Cotter J. Efficacy of crude marijuana and synthetic delta-9-tetrahydrocannabinol as treatment for chemotherapy-induced nausea and vomiting: a systematic literature review. Oncology Nursing Forum 2009; Vol. 36, issue 3:345–52.

**Cronin 1981** *{published data only}*
Cronin CM, Sallan SE, Gelber R, Lucas VS, Laszlo J. Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy. *Journal of Clinical Pharmacology* 1981;**21**(8-9 Suppl):43S–50S.

**Croxford 2003** *{published data only}*
Croxford JL. Therapeutic potential of cannabinoids in CNS disease. *CNS Drugs* 2003;**17**:179–202.

**Cunningham 1985** *{published data only}*
Cunningham D, Forrest GJ, Soukop M. Nabilone and prochlorperazine: a useful combination for emesis induced by cytotoxic drugs. *British Medical Journal* 1985;**291** (6499):864–5.

**Cunningham 1988** *{published data only}*
Cunningham D, Bradley CJ, Forrest GJ, Hutcheon AW, Adams L, Sneddon M, et al. A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. *European Journal of Cancer and Clinical Oncology* 1988;**24**(4):685–9.

**Dalzell 1986** *{published data only}*
Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. *Archives of Disease in Childhood* 1986;**61**(5):502–5.

**Darmani 2010** *{published data only}*
Darmani NA. Cannabinoid-induced hyperemesis: a conundrum-from clinical recognition to basic science mechanisms. *Pharmaceuticals* 2010;**3**(7):2163–77.

**Davis 2007** *{published data only}*
Davis M, Maida V, Daeninck P, Pergolizzi J. The emerging role of cannabinoid neuromodulators in symptom management. *Supportive Care in Cancer* 2007;**15**(1):63–71.

**Davis 2008** *{published data only}*
Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opinion on Investigational Drugs* 2008;**17**(1):85–95.

**Devine 1987** *{published data only}*
Devine ML, Dow GJ, Greenberg BR, Holstein DW, Icaza L, Jue PY, et al. Adverse reactions to delta-9-tetrahydrocannabinol given as an antiemetic in a multicenter study. *Clinical Pharmacy* 1987;**6**(4):319–22.

**Dodds 1985** *{published data only}*
Dodds LJ. The control of cancer chemotherapy-induced nausea and vomiting. *Journal of Clinical Hospital Pharmacy* 1985;**10**(2):143–66.

**Dow 1984** *{published data only}*
Dow GJ, Meyers FH, Stanton W, Devine ML. Serious reactions to oral delta-9-tetrahydrocannabinol in cancer chemotherapy patients. *Clinical Pharmacy* 1984;**3**(1):14.

**Duran 2010** *{published data only}*
Duran M, Perez E, Abanades S, Vidal X, Saura C, Majem M, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *British Journal of Clinical Pharmacology* 2010;**70**(5):656–63.

**Ekert 1979** *{published data only}*
Ekert H, Waters KD, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. *Medical Journal of Australia* 1979;**2**(12):657–9.

**Ettinger 2007** *{published data only}*
Ettinger DS, Bierman PJ, Bradbury B, Comish CC, Ellis G, Ignoffo RJ, et al. Antiemesis: clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network* 2007;**5**(1):12–33.

**Feyer 2011** *{published data only}*
Feyer P, Jordan K. Update and new trends in antiemetic therapy: the continuing need for novel therapies. *Annals of Oncology* 2011;**22**(1):30–8.

**Fiore 1984** *{published data only}*
Fiore JJ, Gralla RJ. Pharmacologic treatment of chemotherapy-induced nausea and vomiting. *Cancer Investigation* 1984;**2**(5):351–61.

**Fox 1979** *{published data only}*
Fox FJ, Baker JJ, Lokey JL. Nabilone as an antiemetic. *New England Journal of Medicine* 1979;**301**(13):728.

**Galal 2009** *{published data only}*
Galal AM, Slade D, Gul W, El-Alfy AT, Ferreira D, Elsohly MA. Naturally occurring and related synthetic cannabinoids and their potential therapeutic applications. *Recent Patents on CNS Drug Discovery* 2009;**4**(2):112–36.

**Gallego 1984** *{published data only}*
Gallego Fernandez C, Ferrandiz Gosalbez JR. Nausea and vomiting induced by cancer chemotherapy. Review of Cannabis and its antiemetic effects. *Farmacia Clinica* 1984; **1**(9):51–62.

**Gerhartz 1983** *{published data only}*
Gerhartz HH, Binsack T, Hiller E. Levonantradol for the treatment of chemotherapy-induced nausea and vomiting. *Klinische Wochenschrift* 1983;**61**(14):719–21.

**Gerra 2010** *{published data only}*
Gerra G, Zaimovic A, Gerra ML, Ciccocioppo R, Cippitelli A, Serpelloni G, et al. Pharmacology and toxicology of Cannabis derivatives and endocannabinoid agonists. *Recent Patents on CNS Drug Discovery* 2010;**5**(1):46–52.

**Goodman 1997** *{published data only}*
Goodman M. Risk factors and antiemetic management of chemotherapy-induced nausea and vomiting. *Oncology Nursing Forum* 1997;**24**(7 Suppl):20–32.

**Gorter 1999** *{published data only}*
Gorter RW. Cancer cachexia and cannabinoids. *Forschende Komplementarmedizin* 1999;**6**(Suppl 3):21–2.

**Grunberg 1989** *{published data only}*
Grunberg SM. Advances in the management of nausea and vomiting induced by non-cisplatin containing chemotherapeutic regimens. *Blood Reviews* 1989;**3**(4): 216–21.

**Guzman 2003** *{published data only}*
Guzman M. Cannabinoids: potential anticancer agents. *Cancer* 2003;**3**(10):745–55.

**Heim 1984** *{published data only}*
Heim ME, Queisser W, Altenburg HP. Randomized crossover study of the antiemetic activity of levonantradol

and metoclopramide in cancer patients receiving chemotherapy. *Cancer Chemotherapy and Pharmacology* 1984;**13**(2):123–5.

**Herrstedt 1998** ***{published data only}***
Herrstedt J, Aapro MS, Smyth JF, Del Favero A. Corticosteroids, dopamine antagonists and other drugs. *Supportive Care in Cancer* 1998;**6**(3):204–14.

**Herrstedt 2008** ***{published data only}***
Herrstedt J. Antiemetics: an update and the MASCC guidelines applied in clinical practice. *Nature Clinical Practice Oncology* 2008;**5**(1):32–43.

**Higi 1982** ***{published data only}***
Higi M, Niederle N, Bremer K, Schmitt G, Schmidt CG, Seeber S. Levonantradol in the treatment of nausea and vomiting caused by cytostatic drugs (author's translation) clinical studies [German]. *Deutsche Medizinische Wochenschrift* 1982;**107**(3):1232–4.

**Hiller 1984** ***{published data only}***
Hiller E, Gerhartz H. New aspects in the antiemetic therapy of cytostatic drug-induced vomiting [German]. *Klinische Wochenschrift* 1984;**62**(10):441–5.

**Hutcheon 1983** ***{published data only}***
Hutcheon AW, Palmer JBD, Soukop M. A randomised multicentre single blind comparison of cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. *European Journal of Cancer and Clinical Oncology* 1983;**19**(8): 1087–90.

**Jordan 2007** ***{published data only}***
Jordan K, Schmoll HJ, Aapro MS. Comparative activity of antiemetic drugs. *Critical Reviews in Oncology-Hematology* 2007;**61**(2):162–75.

**Jordan 2011** ***{published data only}***
Jordan K, Roila F, Molassiotis A, Maranzano E, Clark-Snow RA, Feyer P, et al. Antiemetics in children receiving chemotherapy. MASCC/ESMO guideline update 2009. *Supportive Care in Cancer* 2011;**19**(Suppl 1):S37–42.

**Kearsley 1985** ***{published data only}***
Kearsley JH, Tattersall MH. Recent advances in the prevention or reduction of cytotoxic-induced emesis. *Medical Journal of Australia* 1985;**143**(8):341–6.

**Kenny 1982** ***{published data only}***
Kenny JB, Wilkinson PM. Levonantradol effectiveness in cancer patients resistant to conventional anti-emetics. *Clinical Oncology* 1982;**8**(4):335–9.

**Kluin-Nelemans 1981a** ***{published data only}***
Kluin-Nelemans JC, Meuwissen Th OJA, Nelemans FA, Maes RAA. Tetrahydrocannabinol as antiemetic in patients treated with cytostatics: double blind crossover trial against placebo. *Nederlands Tijdschrift voor Geneeskunde* 1981;**125** (2):900–1.

**Kluin-Nelemans 1981b** ***{published data only}***
Kluin-Nelemans JC, Meuwissen Th OJA, Nelemans FA, Maes RAA. 9-Tetrahydrocannabinol (THC) as an anti-emetic in patients treated with cancer chemotherapy. A double-blind cross-over trial against placebo. *Netherlands Journal of Medicine* 1981;**24**(2):90.

**Krasnow 1991** ***{published data only}***
Krasnow SH. New directions in managing chemotherapy-related emesis. *Oncology* 1991;**5**(9 Suppl):19–24.

**Kreutz 2007** ***{published data only}***
Kreutz S. The magic plant as an antiemetic. Cannabinoids for treatment of nausea and vomiting [German]. *Pharmazie in Unserer Zeit* 2007;**36**(5):389–92.

**Lane 1989** ***{published data only}***
Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JH, Hamm J, et al. Dronabinol and prochlorperazine in combination are better than either single agent alone for treatment of chemotherapy-induced nausea and vomiting. Proceedings of the American Society of Clinical Oncology 1989; Vol. 8:326, Abstract 1269.

**Lane 1990** ***{published data only}***
Lane M, Smith FE, Sullivan RA, Plasse TF. Dronabinol and prochlorperazine alone and in combination as antiemetic agents for cancer chemotherapy. *American Journal of Clinical Oncology: Cancer Clinical Trials* 1990;**13**(6):480–4.

**Laszlo 1982** ***{published data only}***
Laszlo J. Treatment of nausea and vomiting caused by cancer chemotherapy. *Cancer Treatment Reviews* 1982;**9** (Suppl B):3–9.

**Levitt 1981** ***{published data only}***
Levitt M, Wilson A, Bowman D, Kemel S, Krepart G, Marks V, et al. Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications. *Journal of Clinical Pharmacology* 1981;**21**(8-9 Suppl):103S–9S.

**Levitt 1984** ***{published data only}***
Levitt M, Faiman C, Hawks R, Wilson A. Randomized double blind comparison of delta-9-tetrahydrocannabinol and marijuana as chemotherapy antiemetics [abstract]. Proceedings - Annual Meeting of American Society of Clinical Oncology 1984; Vol. 3:91, Abstract C-354.

**Lohr 2008** ***{published data only}***
Lohr L. Chemotherapy-induced nausea and vomiting. *Cancer Journal* 2008;**14**(2):85–93.

**Long 1982** ***{published data only}***
Long A, Mioduszewski JNR. A randomized double-blind cross-over comparison of the antiemetic activity of levonantradol and prochlorperazine. *Proceedings of the American Society of Clinical Oncology* 1982;**1**:C–220.

**Machado 2008** ***{published data only}***
Machado Rocha FC, Stefano SC, De Cassia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *European Journal of Cancer Care* 2008;**17**(5):431–43.

**Mechoulam 1978** ***{published data only}***
Mechoulam R, Carlini EA. Toward drugs derived from cannabis. *Naturwissenschaften* 1978;**65**(4):174–9.

**Mechoulam 1999** *{published data only}*
Mechoulam R. Recent advantages in cannabinoid research. *Forschende Komplementarmedizin* 1999;**6**(Suppl 3):16–20.

**Mechoulam 2001** *{published data only}*
Mechoulam R, Hanus L. The cannabinoids: an overview. Therapeutic implications in vomiting and nausea after cancer chemotherapy, in appetite promotion, in multiple sclerosis and in neuroprotection. *Pain Research and Management* 2001;**6**(2):67–73.

**Meiri 2007** *{published data only}*
Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang HM, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Current Medical Research and Opinion* 2007;**23**(3):533–43.

**Murakami 1986** *{published data only}*
Murakami M, Ota K. Recent advances in the management of chemotherapy-induced emesis [Japanese]. *Japanese Journal of Cancer Chemotherapy* 1986;**13**(3):401–11.

**Musty 2001** *{published data only}*
Musty RE, Rossi R. Effects of smoked cannabis and oral DELTA9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: a review of state clinical trials. Journal of Cannabis Therapeutics 2001; Vol. 1, issue 1:29.

**Nagy 1978** *{published data only}*
Nagy CM, Furnas BA, Einhorn LH, Bond WH. Nabilone (N) anti-emetic crossover study in cancer chemotherapy patients. *American Association for Cancer Research and American Society of Clinical Oncology* 1978;**19**:30.

**Navari 2009a** *{published data only}*
Navari RM. Pharmacological management of chemotherapy-induced nausea and vomiting. *Drugs* 2009; **69**(5):515–33.

**Navari 2009b** *{published data only}*
Navari RM. Antiemetic control: toward a new standard of care for emetogenic chemotherapy. *Expert Opinion on Pharmacotherapy* 2009;**10**(4):629–44.

**Niederle 1986** *{published data only}*
Niederle N, Schutte J, Schmidt CG. Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. *Klinische Wochenschrift* 1986;**64**(8): 362–5.

**Niiranen 1987** *{published data only}*
Niiranen A, Mattson K. Antiemetic efficacy of nabilone and dexamethasone: a randomized study of patients with lung cancer receiving chemotherapy. *American Journal of Clinical Oncology* 1987;**10**(4):325–9.

**Nyman 1982** *{published data only}*
Nyman JV, Fritz WL. A review of the antiemetic use of delta-9-tetrahydrocannabinol and prescribing requirements. *Arizona Medicine* 1982;**39**(1):38–43.

**Orr 1980** *{published data only}*
Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Archives of Internal Medicine* 1980;**140**(11):1431–3.

**Penta 1981** *{published data only}*
Penta JS, Poster DS, Bruno S, Macdonald JS. Clinical trials with antiemetic agents in cancer patients receiving chemotherapy. *Journal of Clinical Pharmacology* 1981;**21**(8-9):11S–22S.

**Perwitasari 2011** *{published data only}*
Perwitasari DA, Gelderblom H, Atthobari J, Mustofa M, Dwiprahasto I, Nortier JWR, et al. Anti-emetic drugs in oncology: pharmacology and individualization by pharmacogenetics. *International Journal of Clinical Pharmacy* 2011;**33**(1):33–43.

**Phillips 2010** *{published data only}*
Phillips RS, Gopaul S, Gibson F, Houghton E, Craig JV, Light K, et al. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: 10.1002/14651858.CD007786.pub2

**Plasse 1991** *{published data only}*
Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacology, Biochemistry and Behavior* 1991;**40**(3): 695–700.

**Porta 2002** *{published data only}*
Porta I, Sales J, Schoenenberger I, Arnaiz JA. Cannabinoids, a myth or a scientific reality?. *Medicina Paliativa* 2002;**9**(3): 129–33.

**Poster 1981** *{published data only}*
Poster DS, Penta JS, Bruno S, Macdonald JS. Delta 9-tetrahydrocannabinol in clinical oncology. *JAMA* 1981;**245** (20):2047–51.

**Reynolds 2002** *{published data only}*
Reynolds R. Comparative efficacy of dronabinol and megestrol acetate. *Journal of Clinical Oncology* 2002;**20**(12): 2912-3; author reply 2913.

**Sallan 1975b** *{published data only}*
Sallan S, Zinberg N, Frei E. Oral delta 9 tetrahydrocannabinol (THC) in the prevention of vomiting (V) associated with cancer chemotherapy (CC). Annual Meeting, proceedings of the American Association for Cancer Research 1975; Vol. 16:575.

**Sallan 1980** *{published data only}*
Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer. A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *New England Journal of Medicine* 1980;**302**(3):135–8.

**Schuette 1985** *{published data only}*
Schuette J, Niederle N, Krischke W. Randomized crossover trial comparing the antiemetic efficacy of nabilone versus alizapride in patients (pts) with nonseminomatous testicular cancer (NSTC) receiving low-dose cisplatin therapy. *Proceedings of the American Association for Cancer Research* 1985;**26**:665.

**Sheidler 1984** *{published data only}*
Sheidler VR, Ettinger DS, Diasio RB, Enterline JP, Brown MD. Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. *Journal of Clinical Pharmacology* 1984; **24**(4):155–9.

**Slatkin 2007** *{published data only}*
Slatkin NE. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting: beyond prevention of acute emesis. *Journal of Supportive Oncology* 2007;**5**(Suppl 3):1–9.

**Smith 2007** *{published data only}*
Smith PF. Will medicinal cannabinoids prove to be useful clinically?. *Current Drug Therapy* 2007;**2**(2):143–50.

**Stambaugh 1982** *{published data only}*
Stambaugh JE, McAdams J, Vreeland F. A phase II randomized trial of the antiemetic activity of levonantradol (CP-50,556) in cancer patients receiving chemotherapy. *Proceedings of the American Society of Clinical Oncology* 1982; **1**:C–240.

**Stambaugh 1984** *{published data only}*
Stambaugh Jr JE, McAdams J, Vreeland F. Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. *Journal of Clinical Pharmacology* 1984;**24**(11-12):480–5.

**Steele 1979** *{published data only}*
Steele N, Braun D, O'Hehir M, Young C. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. Cancer Treatment Reports 1979; Vol. 64, issue 2–3:219–24.

**Stewart 1990** *{published data only}*
Stewart DJ. Cancer therapy, vomiting, and antiemetics. *Canadian Journal of Physiology & Pharmacology* 1990;**68**(2): 304–13.

**Stuart 1982** *{published data only}*
Stuart JFB, Welsh Sangster G, Scullion M, Cash H, Kaye SB, Calman KC. The anti-emetic potential of oral levonantradol in patients receiving cancer chemotherapy. British Journal of Cancer 1982; Vol. 46:492.

**Stuart-Harris 1983** *{published data only}*
Stuart-Harris RC, Mooney CA, Smith IE. Levonantradol: a synthetic cannabinoid in the treatment of severe chemotherapy-induced nausea and vomiting resistant to conventional anti-emetic therapy. *Clinical Oncology* 1983;**9** (2):143–6.

**Sweet 1980** *{published data only}*
Sweet DL. Marijuana for drug-induced nausea and vomiting. *JAMA* 1980;**243**(12):1265.

**Toth 2008** *{published data only}*
Toth J, Szanto J. Prophylaxis of chemotherapy-induced vomiting and nausea [Hungarian]. *Magyar Onkologia* 2008; **52**(4):391–4.

**Tramer 2001** *{published data only}*
Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001;**323**(7303):16–21.

**Ungerleider 1985** *{published data only}*
Ungerleider JT, Sarna G, Fairbanks LA, Goodnight J, Andrysiak T, Jamison K. THC or compazine for the cancer chemotherapy patient - the UCLA study. Part II: patient drug preference. *American Journal of Clinical Oncology* 1985;**8**(2):142–7.

**Venner 1986** *{published data only}*
Venner P, Bruera E, Drebit D, Shankowsky H. Intensive treatment scheduling of nabilone plus dexamethasone (DM) vs metoclopramide plus DM in cisplatin-induced emesis. *Proceedings of the American Society of Clinical Oncology* 1986; **5**:253.

**Vincent 1983** *{published data only}*
Vincent BJ, McQuiston DJ, Einhorn LH. Review of cannabinoids and their antiemetic effectiveness. *Drugs* 1983;**25**(Suppl 1):52–62.

**Voth 1997** *{published data only}*
Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Annals of Internal Medicine* 1997;**126**(10):791–8.

**Wang 2008** *{published data only}*
Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *Canadian Medical Association Journal* 2008;**178**(13):1669–78.

**Ward 1985** *{published data only}*
Ward A, Holmes B. Nabilone. A preliminary review of its pharmacological properties and therapeutic use. *Drugs* 1985;**30**(2):127–44.

**Ware 2008** *{published data only}*
Ware MA, Daeninck P, Maida V. A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting. *Therapeutics and Clinical Risk Management* 2008;**4**(1): 99–107.

**Zuardi 2008** *{published data only}*
Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Revista Brasileira de Psiquiatria* 2008;**30**(3):271–80.

## References to studies awaiting assessment

**Citron 1983** *{published data only}*
Citron ML, Herman TS, Fossieck BE, Krasnow SH, Vreeland F, Harwood S, et al. Double-blind, randomised, crossover study of the antiemetic effect of levonantradol versus tetrahydrocannabinol. *Proceedings of the American Association of Cancer Research* 1983;**24**:165.

**Earhart 1983** *{published data only}*
Earhart RH, Koeller JM. Levonantradol vs prochlorperazine as parenteral antiemetics in cancer patients receiving cisplatin chemotherapy. *Proceedings of the American Association for Cancer Research.* 1983;**24**:163.

**Jhangiani 2005** *{published data only}*
Jhangiani H, Vredenburgh J, Barbato L, Yang H, Yang H M, Baranowski V, et al. Dronabinol or ondansetron alone

and combined for delayed chemotherapy-induced nausea and vomiting (CINV). Abstracts for the 47th Annual Meeting of the American Society of Hematology; 2005 Dec 10-13; Atlanta, Georgia 2005; Vol. 106:477.

**Neidhart 1981** ***{published data only}***

Neidhart JA, Gagen MM, Wilson HE, Young DC. Comparative trial of the antiemetic effects of THC and haloperidol. *Journal of Clinical Pharmacology* 1981;**21**(8-9 Suppl):38S–42S.

## Additional references

**Barowski 1984**

Barowski MT. Advances in anti-emetic therapy. *Cancer Treatment Reviews* 1984;**11**:237–56.

**Basch 2011**

Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology* 2011;**29**(31):4189–96.

**Beusterien 2014**

Beusterien K, Grinspan J, Kuchuk I, Mazzarello S, Dent S, Gertler S, et al. Use of conjoint analysis to assess breast cancer patient preferences for chemotherapy side effects. *Oncologist* 2014;**19**(2):127–34.

**Bonnie 1974**

Bonnie RJ, Whitebread CH. *The Marijuana Conviction: a History of Marijuana Prohibition in the United States*. Charlottesville, VA: University Press of Virginia: The Lindesmith Center, 1974.

**Cohen 1988**

Cohen, J. Statistical power analysis for th ebehavioural sciences. *Statistical power analysis for the behavioural sciences*. 2nd Edition. New Jersey: Lawrence Erlbaum, 1988.

**Darmani 2001**

Darmani NA. Delta(9)-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB (1) receptor antagonist/inverse agonist SR 141716A. *Neuropsychopharmacology* 2001;**24**:198–203.

**de Boer-Dennert 1997**

de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *British Journal of Cancer* 1997;**76**(8):1055–61.

**De Mulder 1992**

De Mulder PHM. Measurement of success: parameters of efficacy. *British Journal of Cancer* 1992;**66**(Suppl XIX):S68.

**Deeks 2001**

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd Edition. London: BMJ, 2001:285–312.

**Devane 1992**

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;**258**:1946–9.

**Dubey 2005**

Dubey S, Brown RL, Esmond SL, Bowers BJ, Healy JM, Schiller JH. Patient preferences in choosing chemotherapy regimens for advanced non-small cell lung cancer. *Journal of Supportive Oncology* 2005;**3**(2):149–54.

**Gralla 1999**

Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *Journal of Clinical Oncology* 1999;**17**(9):2971–94.

**Gralla 2013**

Gralla RJ, Roila F, Tonato M, Herstedt J. MASCC antiemetic guidelines, 2013. www.mascc.org/antiemetic-guidelines (accessed 29 October 2015).

**Grotenhermen 2002**

Grotenhermen F. Effects of cannabis and the cannabinoids. In: Grotenhermen F, Russo E editor(s). *Pharmacology, Toxicology and Therapeutic Potential*. 1st Edition. New York: The Haworth Press, Inc., 2002:55–65.

**Higgins 2003**

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60.

**Higgins 2011**

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

**Huang 2004**

Huang JQ, Zheng GF, Chan GC, Karlberg J, Lam SK, Wong BC. Efficacy of current antiemetic treatments for preventing delayed chemotherapy-induced nausea and vomiting: a meta-analysis of randomized controlled trials. *Clinical Research and Regulatory Affairs* 2004;**21**(3-4): 191–212.

**Ioannidis 2000**

Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. *Journal of Clinical Oncology* 2000;**18**:3409–22.

**Janelsins 2013**

Janelsins MC, Tejani MA, Kamen C, Peoples AR, Mustian KM, Morrow GR. Current pharmacotherapy for chemotherapy-induced nausea and vomiting in cancer patients. *Expert Opinion on Pharmacotherapy* 2013;**14**(6): 757–66.

**Karniol 2001**

Karniol IG. Cannabis sativa and derivatives. In: Seibel SD, Toscano JRA editor(s). *Dependência de Drogas*. 1st Edition. Rio de Janeiro: Atheneu, 2001:131–42.

**Kuchuk 2013**

Kuchuk I, Bouganim N, Beusterien K, Grinspan J, Vandermeer L, Gertler S, et al. Preference weights for

chemotherapy side effects from the perspective of women with breast cancer. *Breast Cancer Research and Treatment* 2013;**142**(1):107.

**Machado Rocha 2008**
Machado Rocha FC, Stefano SC, De Cássia Haiek R, Rosa Oliveira LMQ, da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *European Journal of Cancer Care* 2008;**17**(5):431–43.

**Martin 1992**
Martin M. Myths and realities of antiemetic treatment. *British Journal of Cancer* 1992;**66**(Suppl XIX):S46–51.

**MASCC 1998**
Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). *Annals of Oncology* 1998;**9**(8):811–9.

**Mechoulam 1995**
Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochemical Pharmacology* 1995;**50**:83–90.

**NCCN 2014**
National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) Antiemesis Version 2, 2014. www.nccn.org/professionals/physician_gls/f_guidelines.asp, last retrieved 09.11.15.

**NCCN 2015**
National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Antiemesis Version 2. http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf, last retrieved 09.11.15.

**Olver 1992a**
Olver IN. Methodology in anti-emetic trials. *Oncology* 1992;**49**:269–72.

**Olver 1992b**
Olver IN. Antiemetic study design: desirable objectives, stratifications and analyses. *British Journal of Cancer* 1992;**66**(Suppl XIX):S30–4.

**Olver 2004**
Olver I. Two decades of progress in treating chemotherapy induced emesis. *Cancer Forum* 2004;**28**:140–3.

**Pater 1984**
Pater JL, Willan AR. Methodologic issues in trials of antiemetics. *Journal of Clinical Oncology* 1984;**2**(5):484–7.

**Rhodes 1984**
Rhodes VA, Watson PM, Johnson MH. Development of reliable and valid measures of nausea and vomiting. *Cancer Nursing* 1984;**7**(1):33–41.

**Rodríguez de Fonseca 2005**
Rodríguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. *Alcohol and Alcoholism* 2005;**40(1)**:2–14.

**Roila 2010**
Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Annals of Oncology* 2010;**21**(5):232–43.

**Russo 2014**
Russo S, Cinausero M, Gerratana L, Bozza C, Iacono D, Driol P, et al. Factors affecting patient's perception of anticancer treatments side-effects: an observational study. *Expert Opinion on Drug Safety* 2014;**13**(2):139–50.

**Schwartzberg 2007**
Schwartzberg LS. Chemotherapy-induced nausea and vomiting: clinician and patient perspective. *Journal of Support Oncology* 2007;**5**:5–12.

**Sugiura 1995**
Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochemical and Biophysical Research Communications* 1995;**215**:89–97.

**Sun 2002**
Sun CC, Bodurka DC, Donato ML, Rubenstein EB, Borden CL, Basen-Engquist K, et al. Patient preferences regarding side effects of chemotherapy for ovarian cancer: do they change over time?. *Gynecologic Oncology* 2002;**87**(1):118–28.

**Walsh 2003**
Walsh D, Nelson KA, Mahmoud FA. Established and potential therapeutic applications of cannabinoids in oncology. *Supportive Care in Cancer* 2003;**11**:137–43.

**Wilcox 1982**
Wilcox PM, Fetting JH, Nettesheim KM, Abeloff MD. Anticipatory vomiting in women receiving cyclophosphamide, methotrexate, and 5-FU (CMF) adjuvant chemotherapy for breast carcinoma. *Cancer Treatment Reports* 1982;**66**:1601–4.

* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

### Ahmedzai 1983

| | |
|---|---|
| Methods | Randomised, double-blinded, 2-period cross-over study |
| Participants | 34 people (19 (56%) men/15 (44%) women), median age 58 years. All cannabis naive<br>Tumour types: small cell bronchial carcinoma<br>Chemotherapy regimen: 2 x 21-day cycles. Cyclophosphamide 1 g/$m^2$, doxorubicin 40 mg/$m^2$ and etoposide (VP-16) 100 mg/$m^2$ day 1; etoposide 100 mg/$m^2$ days 2 and 3; vincristine 2 mg with methotrexate 50 mg/$m^2$ day 10 followed by folinic acid rescue. Cyclophosphamide and doxorubicin given IV bolus; VP-16 IV over 1-2 hours<br>Chemotherapy emetogenicity: High |
| Interventions | Nabilone 2 mg orally twice daily x 3 days, n = 34<br>Prochlorperazine 10 mg orally 3 times daily x 3 days, n = 34 |
| Outcomes | Episodes and frequency of nausea and vomiting day 1; withdrawal due to adverse effects; withdrawals due to death; participant preference due to adverse effects; incidence of feeling high, euphoria, postural dizziness, dysphoria |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 8/34 (24%) participants withdrew |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Approximately 10 days' washout period. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Double dummy tablet" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" and dummy tablet used |

**Chang 1979a**

| | |
|---|---|
| Methods | Randomised, double-blind, 3-period cross-over, placebo-controlled trial |
| Participants | 15 people (10/15 (67%) men/5/15 (33%) women) aged 15-49 years (median = 24 years) . 4/15 (27%) participants were cannabis naive<br>Tumour type: osteogenic sarcoma<br>Chemotherapy regimens: methotrexate 250 mg/kg with leucovorin calcium rescue every 3 weeks for 18 months<br>Chemotherapy emetogenicity: low |
| Interventions | Dronabinol 10 mg/$m^2$ orally every 3 hours for total 5 doses (Phase I), n = 15.<br>If participant vomited during this period oral dose was replaced with THC cigarette for remaining doses<br>Placebo, n = 15 |
| Outcomes | Episodes of nausea and vomiting on day of therapy; frequency and severity of nausea; episodes of sedation, euphoria, dizziness, depression, paranoia |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Order of THC-placebo administration was randomized into three paired trials" |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 58/77 (75%) participants received THC, 39/53 (74%) participants received placebo |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Low risk | Groups balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical gelatin capsules with sesame oil". "Identical cigarettes, the odour and taste of a lit placebo cigarette were identical to those of cannabis cigarette" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Chang 1981**

| | |
|---|---|
| Methods | Randomised, double-blind, 3-period cross-over trial |
| Participants | 8 people (6/8 (75%) men/2/8 (25%) women) aged 17-58 years (median = 41 years), 7/8 (88%) participants were cannabis naive<br>Tumour types: resected soft tissue sarcoma<br>Chemotherapy regimen: adjuvant doxorubicin and cyclophosphamide every 4 weeks until a total cumulative doxorubicin dose of 500-550 mg/$m^2$ Doxorubicin (70 mg/$m^2$) and cyclophosphamide (700 mg/$m^2$) were given at constant doses for all participants<br>Chemotherapy emetogenicity: high |
| Interventions | Dronabinol 10 mg/$m^2$ orally every 3 hours for total 5 doses, if vomited then participant given marijuana cigarettes 900 mg, containing THC 1.93% (approximately 17.4 mg), n = 8<br>Placebo, n = 8 |
| Outcomes | Episodes of nausea and vomiting on day of therapy |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Order of THC-placebo administration was randomized into paired trials" |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 17/27 (63%) participants received THC, 16/27 (59%) participants received placebo |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Paired analysis was performed. Unclear if groups balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical gelatin capsules with sesame oil. Identical cigarettes, the odour and taste of a lit placebo cigarette were identical to those of cannabis cigarette" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind". "Neither patients nor nursing staff was [sic] informed which drug was administered" |

**Crawford 1986**

| | |
|---|---|
| Methods | Randomised, 2-period cross-over study |
| Participants | 32 people<br>Tumour type: adenocarcinoma of the ovary or germ cell tumours<br>Chemotherapy regimen: cisplatin 100 mg/m$^2$, cyclophosphamide and doxorubicin (for people with adenocarcinoma of ovary), cisplatin 120 mg/m$^2$, methotrexate and vincristine (for people with germ cell tumours). No information on doses reported<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 1 mg orally every 8 hours, n = 32<br>Metoclopramide 1 mg/kg IV every 3 hours, n = 32 |
| Outcomes | Episodes of vomiting during 24 hours, nausea, dizziness, euphoria and drowsiness |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 7/32 (22%) participants received the 4 planned treatment and only 37/64 (58%) participants received 1 or 2 treatment episodes of nabilone and 39/64 (61%) participants received 1 or 2 treatment episodes of metochlopramide |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | High risk | Assumed washout period sufficient. Paired analysis was not performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Einhorn 1981**

| | |
|---|---|
| Methods | Randomised, prospective, double-blind, 2-period cross-over study |
| Participants | 100 people aged 15-74 years, mean = 28 years<br>Tumour type; sarcoma (1 person), Hodgkin's disease (2 people), lymphoma (4 people), bladder carcinoma (3 people), testicular carcinoma (70 people)<br>Chemotherapy regimens: doxorubicin hydrochloride and cyclophosphamide (1 person), nitrogen mustard, vincristine, prednisone and procarbazine (2 people), cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone (4 people), cisplatin, doxorubicin hydrochloride and 5-fluorouracil (3 people), cisplatin, vinblastine and bleomycin (45 people), cisplatin, vinblastine, bleomycin and doxorubicin hydrochloride (25 people). No information on doses reported<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 2 mg, orally every 6 hours, n = 100<br>Prochlorperazine 10 mg, orally every 6 hours, n = 100 |
| Outcomes | Episodes of nausea and vomiting during 24 hours of therapy; frequency of vomiting; withdrawal due to adverse effects; withdrawal due to early death and change of chemotherapy; episodes of 'feeling high', depression, hallucination, paranoia, hypotension |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Low risk | "Identical capsules used" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 80/100 (80%) participants received nabilone, 80/100 (80%) participants received prochlorperazine |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind", identical capsules used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind", identical capsules used |

**Frytak 1979**

| | |
|---|---|
| Methods | Randomised, double-blind, parallel group trial |
| Participants | 116 people, median age = 61 years. All cannabis naive. THC n = 38 (22 men/16 women) , prochlorperazine n = 41 (21 men/20 women), placebo n = 37 (27 men/10 women)<br>Tumour types: colorectal cancer (28 people), gastric cancer (7 people), liver cancer (2 people), miscellaneous (1 person), gastric surgery (5 people), hepatic metastasis (20 people)<br>Chemotherapy regimens: 5-fluorouracil and semustine or 5-fluorouracil and semustine plus triazinate, razoxane, doxorubicin or vincristine. 5-fluorouracil 300-350 mg/$m^2$ IV for 5 days. Semustine 110-175 mg/$m^2$ day 1 only<br>Chemotherapy emetogenicity: moderate |
| Interventions | Dronabinol 15 mg on day 1, 2 hours prior to chemotherapy, then 2 and 8 hours after initiation of chemotherapy. Then 3 times daily x 3 days orally, n = 38<br>Prochlorperazine 10 mg on day 1, 2 hours prior to chemotherapy, then 2 and 8 hours after initiation of chemotherapy. Then 3 times daily x 3 days orally, n = 41<br>Placebo n = 37 |
| Outcomes | Episodes of nausea and vomiting during 24 hours, sedation, feeling high; withdrawal due to intolerable central nervous system toxicity or excessive vomiting |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Table of random numbers |
| Allocation concealment (selection bias) | Low risk | Drugs dispensed in individual packets identified by code number |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Only 1/117 (0.8%) participants withdrew. After day 1, 10/38 (26%) participants withdrew in THC group, 5/41 (12%) participants withdrew in prochlorperazine group, 3/37 (8%) participants withdrew in placebo group |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Low risk | Groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical opaque gelatin capsules" |

**Frytak 1979** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**George 1983**

| | |
|---|---|
| Methods | Randomized double-blind 2-period cross-over study |
| Participants | 20 people, mean age 54.1 years<br>Tumour type: advanced gynaecological cancer who vomited during the first chemotherapy treatment<br>Chemotherapy regimen: cis-platinum (50 mg/m$^2$) with hydration. Vomited during the first treatment. Doxorubicin (40 mg/m$^2$), cyclophosphamide (600 mg/m$^2$) and cis-platinum (11 people); cyclophosphamide 600 mg and cis-platinum (3 people); cis-platinum (6 people)<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 1 mg 24 hours before chemotherapy then 1 mg 3 times daily orally<br>Chlorpromazine 12.5 mg IM before chemotherapy with additional dose if requested |
| Outcomes | Number of vomiting episodes in 24 hours, participant preference, adverse events |
| Notes | Translated from French |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly allocated by lottery |
| Allocation concealment (selection bias) | Low risk | Identical placebo |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All people were included in the analysis |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Low risk | There was no evident difference caused by the order of administration of the drugs |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Identical placebo, double-dummy tablets used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as double-blind |

**Gralla 1984**

| | |
|---|---|
| Methods | Randomised, double-blinded parallel group trial |
| Participants | 31 people (23 men/ 5 women). THC n = 15 (13 men/2 women), aged 39-72 years (median = 58 years); metoclopramide n = 16 (11 men/5 women), aged 45-70 years (median = 58 years)<br>Tumour types: bronchogenic carcinoma (12 people), oesophageal carcinoma (2 people) , head and neck carcinoma head and neck carcinoma (1 person)<br>Chemotherapy regimens: all receiving first course of cisplatin 120 mg/$m^2$ IV<br>Chemotherapy emetogenicity: high |
| Interventions | Dronabinol 10 mg/$m^2$ 1.5 hours prior to chemotherapy, then at 1.5, 4.5, 7.5 and 10.5 hours after chemotherapy orally, n = 15<br>Metoclopramide, 2 mg/kg 30 minutes prior to chemotherapy, then 1.5, 3.5, 5.5 and 8. 5 hours after chemotherapy IV, n = 16 |
| Outcomes | Episodes of nausea and vomiting during 24 hours, sedation, dizziness, orthostatic hypotension, feeling high |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Paired design in which one patient in every pair was randomly assigned to each treatment" |
| Allocation concealment (selection bias) | Low risk | "Identical vials and capsules used" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 15/15 (100%) participants received THC, 15/16 (94%) participants received metoclopramide |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical vials and capsules used" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Herman 1979**

| | |
|---|---|
| Methods | Randomised, double-blinded, 2-period cross-over study |
| Participants | 152 people (126 men/26 women) aged 15-74 years (median = 33 years)<br>Tumour type: testicular carcinoma (70 people), non-Hodgkin's disease (12 people), Hodgkin's disease (11 people)<br>Chemotherapy regimen: cisplatin daily for 5 days, vinblastine and bleomycin (70 people) ; cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP 12 people); nitrogen mustard (mechlorethamine?), vincristine, procarbazine and prednisone (MOPP 11 people); other regimens included dactinomycin, dacarbazine, 5-fluorouracil, melphalan and nitrosourea compounds. No information on doses reported<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 2 mg, every 8 hours orally, n = 152<br>Prochlorperazine 10 mg, every 8 hours orally, n = 152 |
| Outcomes | Episodes of nausea and vomiting daily during chemotherapy; withdrawal due to adverse effects; episodes of somnolence, dizziness, depression, euphoria, preference |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Low risk | "Drugs packaged in identical containers marked only with a number code" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 113/152 (74%) participants received nabilone, 113/152 (74%) participants received prochlorperazine |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical containers marked only with a number code" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" and "identical containers marked only with a number code" |

**Johansson 1982**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over study |
| Participants | 27 people aged 18-70 years<br>Tumour types: cervical cancer (2 people), cancer of fallopian tubes (2 people), ovarian cancer (13 people), testicular cancer (2 people), head and neck cancer (1 person) , bronchus cancer (1 person), histiocytoma (1 person), fibrosarcoma (1 person), oligodendroma (1 person), lymphoma (2 people)<br>Chemotherapy regimens: doxorubicin 40 mg/$m^2$, cyclophosphamide 500 mg/$m^2$ and cisplatinum 50 mg/$m^2$ (11 people) in combination with vinblastine, vincristine or ftorafur (tegfur-uracil). Cyclophosphamide 750-1000 mg/$m^2$ and cisplatinum 75 mg/$m^2$ when given as sole agents<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 2 mg twice daily x 4 days orally, n = 27<br>Prochlorperazine 10 mg twice daily x 4 days orally, n = 27 |
| Outcomes | Episodes of nausea and vomiting assessed daily and reported for follow-up at end of antiemetic therapy; withdrawal due to lack of efficacy; withdrawal due to hypotension, vertigo and headache; participant preference; episodes of drowsiness, dizziness, depression, hypotension |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 18/27 (67%) participants received nabilone, 18/27 (67%) participants received prochlorperazine |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Jones 1982**

| | |
|---|---|
| Methods | Prospective, randomised, double-blind, 2-period cross-over trial |
| Participants | 54 people; aged 20-37 years (n = 9), 38-57 years (n = 23), > 58 years (n = 22)<br>Tumour types: breast cancer (15 people), lymphoma (12 people), ovarian cancer (8 people), lung cancer (7 people), melanoma (3 people), testicular cancer (2 people), miscellaneous (7 people)<br>Chemotherapy regimens: adriamycin-based regimens (25 people), cisplatinum-based regimens (14 people), other combinations (12 people). No information on doses reported<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 2 mg every 12 hours orally, n = 54<br>Placebo, n = 54 |
| Outcomes | Episodes of nausea and vomiting unclear time period of results unclear; withdrawal due to severe nausea and vomiting; episodes of drowsiness, euphoria, hallucination, hypotension |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 24/54<br>(44%) participants received nabilone, 24/54 (44%) participants received placebo |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Kleinman 1983**

| | |
|---|---|
| Methods | Randomised, double-blind, 4-period cross-over study |
| Participants | 16 people (9 men/7 women) aged 18-53 years (median = 38 years)<br>Tumour types: not reported<br>Chemotherapy regimens: "Cancer chemotherapy known to cause acute gastrointestinal toxicity"<br>Chemotherapy emetogenicity: unable to classify |
| Interventions | Prochlorperazine 10 mg + dronabinol 15 mg x 2 courses orally, n = 16<br>Prochlorperazine + placebo orally, n = 16 |
| Outcomes | Episodes of nausea and vomiting 24 hours after chemotherapy, euphoria, sedation |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 28/32 (87.5%) participants received prochlorperazine + THC, 24/32 (75%) participants received prochlorperazine + placebo (overall 52/64 (81%) participants received either of the 2 courses) |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" and "identical capsules used" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind and identical capsules used" |

**Kluin-Neleman 1979**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over study |
| Participants | 11 people (10 men/1 woman) aged 21-53 years<br>Tumour types: Hodgkin's or non-Hodgkin's lymphoma<br>Chemotherapy regimens: mitoxine 6 mg/$m^2$ (maximum 10 mg), vincristine 1.4 mg/$m^2$ (maximum 2 mg) IV on days 1 and 8. Procarbazine 100 mg/$m^2$ and prednisone 40 mg/$m^2$ oral days 1-14 for 6 cycles with intervals of 2 weeks<br>Chemotherapy emetogenicity: high |
| Interventions | Dronabinol 10 mg/$m^2$ orally, n = 11<br>Placebo, n = 11 |
| Outcomes | Episodes of nausea and vomiting at end of day of therapy, feeling high, dizziness, hallucinations |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 17 participants received THC, 11 participants received placebo |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Washout period 2 weeks. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical gelatin capsules were used" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" and "identical gelatin capsules used" |

**Lane 1991**

| | |
|---|---|
| Methods | Randomised, double-blind, parallel group study |
| Participants | Dronabinol n = 21 (10 men/11 women) aged 20-68 years (median = 47 years), prochlorperazine n = 21 (10 men/11 women) aged 22-64 years (median = 49 years), dronabinol plus prochlorperazine n = 20 (9 men/11 women) aged 25-65 years (median = 55.5 years) . Total n = 62 (29 men/33 women) aged 20-68 years (median = 52 years)<br>All cannabis naive<br>Tumour types: breast cancer (24 people), colon cancer (3 people), lung cancer (8 people) , lymphoma (17 people), miscellaneous (10 people)<br>Chemotherapy regimens: cyclophosphamide and doxorubicin (26 people), 5-fluorouracil (14 people), vincristine (13 people), etoposide (10 people), No information on doses reported. 48/62 participants received chemotherapy with high emetogenic potential<br>Chemotherapy emetogenicity: unable to classify |
| Interventions | Dronabinol 10 mg every 6 hours orally, n = 21<br>Prochlorperazine 10 mg every 6 hours orally, n = 21<br>Dronabinol 10 mg + prochlorperazine 10 mg orally, n = 20 |
| Outcomes | Episodes of nausea and vomiting during chemotherapy treatment; withdrawal due to adverse effects; episodes of somnolence, dizziness, paranoid reaction, depression |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 17/21 (81%) participants received dronabinol, 20/21 (95%) participants received prochlorperazine, 17/20 (85%) participants received dronabinol + prochlorperazine |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Low risk | Groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" |

**Lane 1991** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Levitt 1982**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over study |
| Participants | 58 people aged 17-78 years<br>Tumour types: lung cancer (21 people), ovarian cancer (11 people), breast cancer (10 people), other cancers (16 people)<br>Chemotherapy regimens: combinations of doxorubicin, bleomycin, cisplatinum, cyclophosphamide, dactinomycin, melphalan, mitomycin C, methotrexate, vincristine, etoposide, 5-fluorouracil. No information on doses reported<br>Chemotherapy emetogenicity: unable to classify |
| Interventions | Nabilone, n = 58<br>Placebo, n = 58 |
| Outcomes | Episodes of nausea and vomiting time of assessment unclear, frequency and severity of nausea, withdrawal due to lack of efficacy, adverse effects, episodes of drowsiness |
| Notes | Dose and duration not reported |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 36/58<br>(62%) participants received nabilone, 36/58 (62%) participants received placebo |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" |

**Levitt 1982** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**McCabe 1988**

| | |
|---|---|
| Methods | Randomised, 2-period cross-over trial |
| Participants | 36 (9 men/27 women) aged 18-69 years (median = 48 years)<br>Tumour types: breast cancer (11 people), haematological malignancies (9 people), sarcomas (6 people), gastrointestinal malignancies (5 people), melanoma (2 people), ovarian cancer (2 people), testicular cancer (1 person)<br>Chemotherapy regimens: doxorubicin (13 people), cyclophosphamide, methotrexate and 5-fluorouracil (7 people), nitrogen mustard, vincristine, procarbazine and prednisone (7 people), platinum combinations (4 people), DTIC (2 people), 5-fluorouracil combinations (2 people), 5-azacytadine (1 person). No information on doses reported<br>Chemotherapy emetogenicity: moderate to high |
| Interventions | Dronabinol 15 mg/m$^2$ 1 hour prior to chemotherapy, then every 4 hours for 24 hours after chemotherapy orally, n = 36<br>Prochlorperazine 10 mg 1 hour prior to chemotherapy, then every 4 hours for 24 hours after chemotherapy orally, n = 36 |
| Outcomes | Episodes of nausea and vomiting during 24 hours, feeling high, dizziness, dysphoria, hallucination, paranoia |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All people were analysed |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |

**McCabe 1988** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | "Blinding not achieved" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Study not blinded |

**Niiranen 1985**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over study |
| Participants | 32 people (20 men/4 women) aged 48-78 years, mean = 61 years<br>Tumour type: lung cancer<br>Chemotherapy regimen: cyclophosphamide 1.2 g/$m^2$ day 1, etoposide 150 mg/$m^2$ IV day 1, 250 mg/$m^2$ orally day 3, and vincristine 1.3 mg/$m^2$ days 1 and 8 (5 people); cyclophosphamide 400 mg/$m^2$, adriamycin 40 mg/$m^2$, cisplatinum 40 mg/$m^2$ every 28 days (8 people); cisplatinum 90 mg/$m^2$ day 1 and vindesine 3 mg/$m^2$ 5 x weekly then twice monthly every 28 days (2 people); cisplatinum 90 mg/$m^2$ day 1 and etoposide 50 mg/$m^2$ days 1-5 every 28 days (9 people); cisplatinum 60 mg/$m^2$ day 1 and etoposide 150 mg/$m^2$ IV day 1 and 200 mg/$m^2$ orally day 3 every 28 days (1 person)<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 1 mg orally night before chemotherapy, 1 hour before chemotherapy and every 12 hours up to 24 hours as required orally, n = 32<br>Prochlorperazine 7.5 mg orally night before chemotherapy, 1 hour before chemotherapy and every 12 hours up to 24 hours as required orally, n = 32 |
| Outcomes | Episodes, frequency and severity of nausea and vomiting at 24 hours; withdrawal due to adverse effects; participant preference; episodes of drowsiness, hallucination, hypotension |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 24/32 (75%) participants received nabilone, 24/32 (75%) participants received prochlorperazine |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |

**Niiranen 1985** (*Continued*)

| | | |
|---|---|---|
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical appearing capsules used" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" and "identical appearing capsules used" |

**Orr 1981**

| | |
|---|---|
| Methods | Randomised double-blind 2-period cross-over |
| Participants | 79 people (28 men/51 women) aged 22-71 years, mean = 46 years<br>Tumour type: variety of neoplasms<br>Chemotherapy regimen: doxorubicin, cyclophosphamide, 5-fluorouracil (with methotrexate), nitrogen mustard, imidazole carboxamide, nitrosaurea and cytosine arabinoside. No information on doses reported<br>Chemotherapy emetogenicity: high (5-fluorouracil + methotrexate low risk but only 3/55 people) |
| Interventions | Dronabinol 7 mg/m$^2$ every 4 hours x 4 doses orally, n = 79<br>Prochlorperazine 7 mg every 4 hours x 4 doses orally, n = 79 |
| Outcomes | Nausea 24 hours post treatment and adverse events |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 55/79 (69%) participants in both groups analysed |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Un- |

**Orr 1981** (*Continued*)

| | | |
|---|---|---|
| | | clear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical capsule used" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | States "double-blind" |

**Pomeroy 1986**

| | |
|---|---|
| Methods | Randomised, double-blind parallel group trial |
| Participants | 38 people (23 men/15 women) aged 21-66 years (median = 42 years)<br>Tumour types: ovarian cancer (11 people), testicular cancer (9 people), bronchus carcinoma (8 people), non-Hodgkin's lymphoma (3 people), Hodgkin's disease (2 people), sarcoma (2 people), breast cancer (1 person), melanoma (1 person), nephroblastoma (1 person)<br>Chemotherapy regimens: cisplatin (10 people); cisplatin and treosulphan (7 people) ; cisplatin, vincristine, methotrexate and bleomycin (4 people), cisplatin, actinomycin D and etoposide (2 people); cisplatin, vinblastine and bleomycin (2 people); cisplatin and vindesine (1 person); adriamycin, bleomycin, vincristine and DTIC (2 people); adriamycin, vincristine and cyclophosphamide (2 people); adriamycin, vincristine, cyclophosphamide and prednisone (2 people); adriamycin, vincristine and etoposide (1 person); ifosfamide (2 people); vincristine, methotrexate and 5-fluorouracil (1 person); vindesine, DTIC and 1-(2-chloroethyl)3-cyclohexyl-1-nitrosurea (CCNU) (1 person). No information on doses reported<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 1 mg 3 times daily x 2 cycles orally, n = 19<br>Domperidone 20 mg 3 times daily x 2 cycles orally, n = 19 |
| Outcomes | Episodes of vomiting daily, withdrawal due to adverse effects, lack of efficacy, episodes of drowsiness, dizziness, hypotension, euphoria |
| Notes | 2 cycles of chemotherapy evaluated |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |

**Pomeroy 1986** (*Continued*)

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 32/38 (84%) participants received nabilone, 33/38 (87%) participants received domperidone |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical capsules used" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" and "identical capsules used" |

**Sallan 1975a**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over study |
| Participants | 22 people (10 men/12 women) aged 18-76 years (median = 29.5 years)<br>Tumour types: variety of neoplasms<br>Chemotherapy regimen: adriamycin, 5-azacytidine, nitrogen mustard, imidazole carboxamide, procarbazine, high-dose cyclophosphamide or high-dose methotrexate or combinations. No information on doses reported<br>Chemotherapy emetogenicity: unable to classify |
| Interventions | Dronabinol 15 mg, later changed to 10 mg/$m^2$, every 4 hours x 3 doses orally, n = 33<br>Placebo, n = 33 |
| Outcomes | Episodes of nausea and vomiting on day after treatment, withdrawal due to adverse effects, episodes of feeling high, somnolence, paranoia, hallucination |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 20/33 (61%) participants received THC, 22/33 (67%) participants received placebo |

**Sallan 1975a** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Identical gelatin capsules used" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" and "identical gelatin capsules used" |

**Steele 1980**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over study |
| Participants | 55 people aged 19-65 years<br>Tumour types: not reported<br>Chemotherapy regimen: high-dose *cis*-dichlorodiammineplatinum 120 mg/$m^2$ ± vindesine 3 mg/$m^2$ every 4-6 weeks; low-dose *cis*-dichlorodiammineplatinum 60 mg/$m^2$ ± vindesine 3 mg/$m^2$, every 4-6 weeks; low-dose *cis*-dichlorodiammineplatinum 60 mg/$m^2$ ± adriamycin 45 mg/$m^2$ every 3-4 weeks; mechlorethamine 6 mg/$m^2$ + vincristine 1.4 mg/$m^2$ + procarbazine orally x 14 days 100 mg/$m^2$ every 4 weeks days 1-8; streptozotocin 500 mg/$m^2$ every week; actinomycin D 1 mg/$m^2$ ± vinblastine 4 mg/$m_2$ + chlorambucil orally x 14 days 4 mg/$m^2$ or 0.15 mg/kg every 3-4 weeks; DTIC 800 mg/$m^2$ ± cyclophosphamide orally x 14 days 100 mg/$m^2$ every 4 weeks. All drugs IV unless otherwise stated<br>Chemotherapy emetogenicity: high |
| Interventions | Nabilone 2 mg every 12 hours x 3-5 doses orally, n = 55<br>Prochlorperazine 10 mg every 12 hours x 3-5 doses orally, n = 55 |
| Outcomes | Episodes of nausea and vomiting during 24 hours; withdrawal due to adverse effects; lack of efficacy, episodes of somnolence, dizziness, feeling high, postural hypotension, dysphoria, hallucination |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |

**Steele 1980** (*Continued*)

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 37/55 (67%) participants received nabilone, 37/55 (67%) participants received prochlorperazine |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Ungerleider 1982**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over study |
| Participants | 214 people (107 men/107 women) aged 18-82 years (median = 47 years)<br>Tumour types: "wide variety of neoplasms"<br>Chemotherapy regimens: antibiotics (70 people), nitrosoureas (21 people), alkylating agents (119 people), antimetabolites (82 people), vinca-alkaloids (60 people), hormones (13 people), miscellaneous (33 people) and combinations. Rated as high for 66% of people, moderate for 27% of people or low for 7% of people emetic potential<br>Chemotherapy emetogenicity: unable to classify - unknown combinations |
| Interventions | Dronabinol 7.5 mg for < 1.4/$m^2$, 10 mg for 1.4-1.8 $m^2$ or 12.5 mg for > 1.8 $m^2$ orally, n = 214<br>Prochlorperazine 10 mg 1 hour prior to chemotherapy, then every 4 hours x 4 doses per day x all chemotherapy days orally, n = 214 |
| Outcomes | Episodes of nausea and vomiting during 24 hours; withdrawal due to adverse effects; episodes of sedation, depression, feeling high |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Table of random numbers |

**Ungerleider 1982** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 172/214 (80%) participants received THC, 181/214 (85%) received prochlorperazine |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Low risk | Washout period 1-3 weeks. Paired analysis was performed. Groups were balanced at baseline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Reported as "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

**Wada 1982**

| | |
|---|---|
| Methods | Randomised, double-blind, 2-period cross-over trial |
| Participants | 114 people (47 men/67 women) aged 18-81 years (median = 57 years)<br>Tumour types: lung cancer (23 people), breast cancer (18 people), ovarian cancer (16 people), lymphoma (including Hodgkin's) (12 people), colonic cancer (7 people), prostatic cancer (5 people), adenocarcinoma (5 people), bladder cancer (3 people), melanoma (3 people), pancreatic cancer (3 people), oesophageal cancer (3 people), stomach cancer (3 people), sarcoma (2 people), testicular cancer (2 people), others (9 people)<br>Chemotherapy regimens: adriamycin (66 people), carmustine (2 people), bleomycin (7 people), cisplatinum (40 people), cytoxan (46 people), dactinomycin (1 person), DTIC (7 people), 5-fluorouracil (29 people), mustine (4 people), MCCNU (6 people), melphalan (1 person), methotrexate (14 people), mitomycin (17 person), procarbazine (7 people), streptozotocin (1 person), tamoxifen (1 person), vinblastine (5 person), vincristine (16 people), VP-16 (1 person) |
| Interventions | Nabilone 2 mg night prior and 1-3 hours before chemotherapy and then every 12 hours orally, n = 114<br>Placebo, n = 114 |
| Outcomes | Episodes of nausea and vomiting during 24 hours; withdrawal due to adverse effects; lack of efficacy; progressive disease; death; participant preference; episodes of dizziness, drowsiness, euphoria, dysphoria, hypotension, hallucination |
| Notes | |

***Risk of bias***

**Wada 1982** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | 84/114 (74%) participants completed both the courses, 92/114 (81%) participants were evaluable for efficacy |
| Selective reporting (reporting bias) | Low risk | Data reported for primary outcome |
| Other bias | Unclear risk | Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Reported as "double-blind" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Blinding assumed as study reported as "double-blind" |

DTIC: 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide; HN2: ; IM: intramuscular; IV: intravenous; MCCNU: methyl lomustine; n: number; THC: delta-9-tetrahydrocannabinol.

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Aapro 1981 | Not a primary study - editorial |
| Allan 1987 | Not a primary study - review |
| Anderson 1981 | Not a primary study - review |
| Artim 1983 | Participants received chemotherapy and radiotherapy |
| Bateman 1982 | Not a primary study - letter |
| Ben 2006 | Not a primary study - review |

(*Continued*)

| | |
|---|---|
| Biedrzycki 2007 | Not a primary study - conference presentation |
| Broder 1982 | Lacks data - abstract of preliminary findings, participant age and characteristics not reported |
| Carey 1983 | Not a primary study - review |
| Chan 1987 | Randomised controlled trial involving children |
| Chang 1979b | Duplicate of Chang 1979a |
| Citron 1985 | Cross route comparison of intramuscular versus oral cannabinoid |
| Cocchetto 1981 | Not a primary study - review |
| Colls 1980a | Letter - lacks detail on study methods, participant groups, control intervention and results |
| Colls 1980b | Did not report data for primary outcome, measurement of nausea and vomiting using a non-validated measure. No details on participants reported |
| Cone 1982 | Not randomised - single-arm study |
| Costa 2007 | Not a primary study - review |
| Cotter 2009 | Not a primary study - review |
| Cronin 1981 | Not randomised - single-arm cross-over study |
| Croxford 2003 | Not a primary study - review |
| Cunningham 1985 | Control group was cannabinoid monotherapy and not conventional anti-emetic |
| Cunningham 1988 | Sub-therapeutic dose of prochlorperazine used |
| Dalzell 1986 | Randomised controlled trial involving children |
| Darmani 2010 | Not a primary study - review |
| Davis 2007 | Not a primary study - review |
| Davis 2008 | Not a primary study - review |
| Devine 1987 | Not randomised - single-arm cross-over study |
| Dodds 1985 | Not a primary study - review from thesis |
| Dow 1984 | Not a primary study - letter |

(*Continued*)

| | |
|---|---|
| Duran 2010 | Not an approved formulation of delta-9-tetrahydrocannabinol |
| Ekert 1979 | Randomised controlled trial involved children not adults |
| Ettinger 2007 | Not a primary study - clinical practice guidelines |
| Feyer 2011 | Not a primary study - review |
| Fiore 1984 | Not a primary study - review |
| Fox 1979 | Not a primary study - letter |
| Galal 2009 | Not a primary study - review |
| Gallego 1984 | Not a primary study - review |
| Gerhartz 1983 | Not randomised - single-arm study |
| Gerra 2010 | Not a primary study - review |
| Goodman 1997 | Not a primary study - review |
| Gorter 1999 | Not randomised |
| Grunberg 1989 | Not a primary study - review |
| Guzman 2003 | Not a primary study - review |
| Heim 1984 | Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol |
| Herrstedt 1998 | Not a primary study - review |
| Herrstedt 2008 | Not a primary study - review |
| Higi 1982 | Pilot study |
| Hiller 1984 | Not a primary study - review |
| Hutcheon 1983 | Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol |
| Jordan 2007 | Not a primary study - review |
| Jordan 2011 | Not a primary study - review guideline |
| Kearsley 1985 | Not a primary study - review |
| Kenny 1982 | Non-randomised single-arm study |

(*Continued*)

| | |
|---|---|
| Kluin-Nelemans 1981a | Duplicate to included |
| Kluin-Nelemans 1981b | Not randomised. Abstract with scant details of methods reported |
| Krasnow 1991 | Not a primary study - review |
| Kreutz 2007 | Not a primary study - review |
| Lane 1989 | Duplicate Lane 1991 |
| Lane 1990 | Duplicate data. Single-centre study included in Lane 1991 |
| Laszlo 1982 | Not a primary study - review |
| Levitt 1981 | Evaluates ophthalmological outcomes. Nausea and vomiting not evaluated |
| Levitt 1984 | Cross-route comparison of oral versus smoked cannabis |
| Lohr 2008 | Not a primary study - review |
| Long 1982 | Preliminary data presented |
| Machado 2008 | Not a primary study - systematic review and meta-analysis |
| Mechoulam 1978 | Not a primary study - drug development |
| Mechoulam 1999 | Not a primary study - review |
| Mechoulam 2001 | Not a primary study - review |
| Meiri 2007 | Not acute nausea and vomiting but evaluating delayed nausea and vomiting |
| Murakami 1986 | Not a primary study - review |
| Musty 2001 | Not a primary study - review |
| Nagy 1978 | Scanty data in an abstract - no extractable data |
| Navari 2009a | Not a primary study - review |
| Navari 2009b | Not a primary study - review |
| Niederle 1986 | Evaluates a non-eligible anti-emetic (alizapride) |
| Niiranen 1987 | Control group was cannabinoid monotherapy and not conventional anti-emetic |

(*Continued*)

| | |
|---|---|
| Nyman 1982 | Not a primary study - review |
| Orr 1980 | Duplicate of Orr 1981 |
| Penta 1981 | Not a primary study - review |
| Perwitasari 2011 | Not a primary study - review |
| Phillips 2010 | Not a primary study - review |
| Plasse 1991 | Not a primary study - expert opinion |
| Porta 2002 | Not a primary study - review |
| Poster 1981 | Not a primary study - review |
| Reynolds 2002 | Not a primary study - letter |
| Sallan 1975b | Duplicate study of Sallan 1975a |
| Sallan 1980 | Participants aged 9-70 years; number or percent of children included not reported |
| Schuette 1985 | Duplicate study reported in Niederle 1986 |
| Sheidler 1984 | Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol |
| Slatkin 2007 | Not a primary study - review |
| Smith 2007 | Not a primary study - review |
| Stambaugh 1982 | Cross-route comparison of intramuscular versus oral cannabinoid |
| Stambaugh 1984 | Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol |
| Steele 1979 | Duplicate study reported in Steele 1980 |
| Stewart 1990 | Not a primary study - review |
| Stuart 1982 | Not randomised - single-arm study |
| Stuart-Harris 1983 | Not randomised |
| Sweet 1980 | Not a primary study - letter |
| Toth 2008 | Not a primary study - review |
| Tramer 2001 | Not a primary study - review |

(*Continued*)

| | |
|---|---|
| Ungerleider 1985 | Sub-group analysis of study reported in Ungerleider 1982 |
| Venner 1986 | Preliminary results - ongoing study |
| Vincent 1983 | Not a primary study - review |
| Voth 1997 | Not a primary study - review |
| Wang 2008 | Not a primary study - review |
| Ward 1985 | Not a primary study - drug evaluation |
| Ware 2008 | Not a primary study - review |
| Zuardi 2008 | Not a primary study - review |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

### Citron 1983

| | |
|---|---|
| Methods | Double-blind, randomised, crossover study |
| Participants | People reciveing chemotherapy |
| Interventions | IM levonantradol, a synthetic cannabinoid, given at a dose of 1 mg every 4 hours versus oral delta-9-tetrahydro-cannabinol (THC) given at a dose of 15 mg every 4 hours |
| Outcomes | Nausea, emetic episodes |
| Notes | |

### Earhart 1983

| | |
|---|---|
| Methods | RCT |
| Participants | Cancer patients receiving cisplatin chemotherapy |
| Interventions | Evonantradol versus prochlorperazine as parenteral antiemetics |
| Outcomes | Nausea and vomiting |
| Notes | |

**Jhangiani 2005**

| | |
|---|---|
| Methods | Double-blind, placebo-controlled study |
| Participants | Patients receiving moderately to highly emetogenic chemotherapy |
| Interventions | Dronabinol alone or in combination with ondansetron versus ondansetron alone |
| Outcomes | Nausea and vomiting intensity |
| Notes | |

**Neidhart 1981**

| | |
|---|---|
| Methods | A prospective, randomized and double-blinded trial |
| Participants | All patients are receiving chemotherapeutic agents known to induce severe vomiting |
| Interventions | Effects of delta-9-tetrahydrocannabinol and haloperidol |
| Outcomes | Nausea and vomiting |
| Notes | |

## DATA AND ANALYSES

### Comparison 1. Cannabinoid versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Absence of nausea | 2 | 96 | Risk Ratio (IV, Random, 95% CI) | 2.0 [0.19, 20.97] |
| 2 Absence of vomiting | 3 | 168 | Risk Ratio (IV, Random, 95% CI) | 5.69 [2.56, 12.64] |
| 2.1 Nabilone | 1 | 72 | Risk Ratio (IV, Random, 95% CI) | 7.25 [2.84, 18.52] |
| 2.2 Dronabinol | 2 | 96 | Risk Ratio (IV, Random, 95% CI) | 3.0 [0.65, 13.76] |
| 3 Absence of nausea and vomiting | 3 | 288 | Risk Ratio (IV, Random, 95% CI) | 2.86 [1.76, 4.65] |
| 3.1 Cannabis naive | 1 | 75 | Risk Ratio (IV, Random, 95% CI) | 2.23 [1.04, 4.78] |
| 3.2 Prior cannabis use | 2 | 213 | Risk Ratio (IV, Random, 95% CI) | 3.40 [1.80, 6.39] |
| 4 Depression | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 5 Dysphoria | 2 | 96 | Risk Ratio (IV, Random, 95% CI) | 9.00 [0.50, 160.59] |
| 6 'Feeling high' | 3 | 137 | Risk Ratio (IV, Random, 95% CI) | 31.10 [6.37, 151.85] |
| 7 Paranoia | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 8 Sedation | 2 | 139 | Risk Ratio (IV, Random, 95% CI) | 4.47 [0.35, 57.81] |
| 9 Participant preference | 2 | 256 | Risk Ratio (IV, Random, 95% CI) | 4.82 [1.74, 13.36] |
| 10 Withdrawal for any reason | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 11 Withdrawal due to adverse event | 2 | 276 | Risk Ratio (IV, Random, 95% CI) | 6.85 [1.96, 23.99] |
| 12 Withdrawal due to lack of efficacy | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |

### Comparison 2. Cannabinoid versus other anti-emetic agent

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Absence of nausea | 5 | 258 | Risk Ratio (IV, Random, 95% CI) | 1.46 [0.67, 3.15] |
| 1.1 Prochlorperazine | 5 | 258 | Risk Ratio (IV, Random, 95% CI) | 1.46 [0.67, 3.15] |
| 2 Absence of nausea (subgroup analysis 2) | 5 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 2.1 Nabilone | 3 | 141 | Risk Ratio (IV, Random, 95% CI) | 1.41 [0.33, 6.03] |
| 2.2 Dronabinol | 2 | 117 | Risk Ratio (IV, Random, 95% CI) | 2.38 [0.21, 26.91] |
| 3 Absence of vomiting | 4 | 209 | Risk Ratio (IV, Random, 95% CI) | 1.11 [0.86, 1.44] |
| 3.1 Prochlorperazine | 4 | 209 | Risk Ratio (IV, Random, 95% CI) | 1.11 [0.86, 1.44] |
| 4 Absence of vomiting (subgroup analysis 2) | 4 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 4.1 Nabilone | 2 | 93 | Risk Ratio (IV, Random, 95% CI) | 1.55 [0.39, 6.24] |
| 4.2 Dronabinol | 2 | 116 | Risk Ratio (IV, Random, 95% CI) | 1.05 [0.64, 1.71] |
| 5 Absence of nausea and vomiting | 4 | 414 | Risk Ratio (IV, Random, 95% CI) | 2.00 [0.74, 5.38] |
| 5.1 Prochlorperazine | 4 | 414 | Risk Ratio (IV, Random, 95% CI) | 2.00 [0.74, 5.38] |
| 6 Absence of nausea and vomiting (subgroup analysis 1) | 4 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |

| | | | | |
|---|---|---|---|---|
| 6.1 Cannabis naive | 2 | 116 | Risk Ratio (IV, Random, 95% CI) | 1.10 [0.70, 1.72] |
| 6.2 Prior cannabis use | 2 | 298 | Risk Ratio (IV, Random, 95% CI) | 17.98 [2.44, 132.43] |
| 7 Absence of nausea and vomiting (subgroup analysis 2) | 4 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 7.1 Nabilone | 1 | 226 | Risk Ratio (IV, Random, 95% CI) | 17.0 [0.99, 291.06] |
| 7.2 Dronabinol | 3 | 188 | Risk Ratio (IV, Random, 95% CI) | 1.44 [0.62, 3.31] |
| 8 Dizziness | 9 | 743 | Risk Ratio (IV, Random, 95% CI) | 2.54 [1.91, 3.37] |
| 8.1 Domperidone | 1 | 38 | Risk Ratio (IV, Random, 95% CI) | 2.75 [1.06, 7.12] |
| 8.2 Prochlorperazine | 7 | 675 | Risk Ratio (IV, Random, 95% CI) | 2.36 [1.82, 3.07] |
| 8.3 Metoclopramide | 1 | 30 | Risk Ratio (IV, Random, 95% CI) | 12.0 [1.78, 81.06] |
| 9 Dysphoria | 3 | 192 | Risk Ratio (IV, Random, 95% CI) | 7.17 [1.33, 38.84] |
| 9.1 Prochloperazine | 3 | 192 | Risk Ratio (IV, Random, 95% CI) | 7.17 [1.33, 38.84] |
| 10 Euphoria | 4 | 358 | Risk Ratio (IV, Random, 95% CI) | 8.89 [2.05, 38.63] |
| 10.1 Domperidone | 1 | 38 | Risk Ratio (IV, Random, 95% CI) | 5.0 [0.26, 97.70] |
| 10.2 Prochlorperazine | 2 | 280 | Risk Ratio (IV, Random, 95% CI) | 17.97 [2.42, 133.37] |
| 10.3 Chlorpromazine | 1 | 40 | Risk Ratio (IV, Random, 95% CI) | 3.0 [0.13, 69.52] |
| 11 'Feeling high' | 5 | 419 | Risk Ratio (IV, Random, 95% CI) | 5.90 [3.42, 10.17] |
| 11.1 Prochlorperazine | 4 | 389 | Risk Ratio (IV, Random, 95% CI) | 6.18 [3.52, 10.85] |
| 11.2 Metoclopramide | 1 | 30 | Risk Ratio (IV, Random, 95% CI) | 3.0 [0.35, 25.68] |
| 12 Hallucinations | 2 | 144 | Risk Ratio (IV, Random, 95% CI) | 5.39 [0.66, 43.68] |
| 12.1 Prochlorperazine | 2 | 144 | Risk Ratio (IV, Random, 95% CI) | 5.39 [0.66, 43.68] |
| 13 Postural hypotension | 6 | 413 | Risk Ratio (IV, Random, 95% CI) | 2.40 [0.88, 6.53] |
| 13.1 Domperidone | 1 | 38 | Risk Ratio (IV, Random, 95% CI) | 4.0 [0.49, 32.57] |
| 13.2 Prochlorperazine | 3 | 305 | Risk Ratio (IV, Random, 95% CI) | 1.22 [0.52, 2.89] |
| 13.3 Metoclopramide | 1 | 30 | Risk Ratio (IV, Random, 95% CI) | 17.0 [1.07, 270.41] |
| 13.4 Chlorpromazine | 1 | 40 | Risk Ratio (IV, Random, 95% CI) | 7.0 [0.95, 51.80] |
| 14 Paranoia | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 14.1 Prochlorperazine | 1 | 42 | Risk Ratio (IV, Random, 95% CI) | 3.0 [0.13, 69.70] |
| 15 Sedation | 11 | 1055 | Risk Ratio (IV, Random, 95% CI) | 1.33 [1.08, 1.64] |
| 15.1 Domperidone | 1 | 38 | Risk Ratio (IV, Random, 95% CI) | 1.22 [0.66, 2.25] |
| 15.2 Prochlorperazine | 8 | 947 | Risk Ratio (IV, Random, 95% CI) | 1.44 [1.18, 1.76] |
| 15.3 Metoclopramide | 1 | 30 | Risk Ratio (IV, Random, 95% CI) | 0.93 [0.73, 1.18] |
| 15.4 Chlorpromazine | 1 | 40 | Risk Ratio (IV, Random, 95% CI) | 1.71 [0.85, 3.44] |
| 16 Depression | 3 | 317 | Risk Ratio (IV, Random, 95% CI) | 0.81 [0.51, 1.28] |
| 16.1 Prochlorperazine | 3 | 317 | Risk Ratio (IV, Random, 95% CI) | 0.81 [0.51, 1.28] |
| 17 Participant preference | 9 | 799 | Risk Ratio (IV, Random, 95% CI) | 2.76 [1.88, 4.03] |
| 17.1 Prochlorperazine | 7 | 695 | Risk Ratio (IV, Random, 95% CI) | 3.24 [2.23, 4.72] |
| 17.2 Metoclopramide | 1 | 64 | Risk Ratio (IV, Random, 95% CI) | 1.2 [0.61, 2.37] |
| 17.3 Chlorpromazine | 1 | 40 | Risk Ratio (IV, Random, 95% CI) | 2.0 [0.83, 4.81] |
| 18 Withdrawal for any reason | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 18.1 Prochlorperazine | 1 | 42 | Risk Ratio (IV, Random, 95% CI) | 3.5 [1.38, 8.89] |
| 19 Withdrawal due to adverse event | 6 | 740 | Risk Ratio (IV, Random, 95% CI) | 3.16 [1.26, 7.93] |
| 19.1 Domperidone | 1 | 76 | Risk Ratio (IV, Random, 95% CI) | 3.0 [0.13, 71.40] |
| 19.2 Prochlorperazine | 5 | 664 | Risk Ratio (IV, Random, 95% CI) | 3.90 [1.25, 12.20] |
| 20 Withdrawal due to lack of efficacy | 2 | 118 | Risk Ratio (IV, Random, 95% CI) | 0.97 [0.04, 20.93] |
| 20.1 Domperidone | 1 | 76 | Risk Ratio (IV, Random, 95% CI) | 0.14 [0.01, 2.67] |
| 20.2 Prochlorperazine | 1 | 42 | Risk Ratio (IV, Random, 95% CI) | 3.5 [1.38, 8.89] |

## Comparison 3. Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Absence of nausea | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 2 Absence of vomiting | 2 | 89 | Risk Ratio (IV, Random, 95% CI) | 1.47 [0.69, 3.13] |
| 3 Absence of nausea and vomiting | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 4 Depression | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 5 Dizziness | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 6 Dysphoria | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 7 Paranoia | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 8 Sedation | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 9 Withdrawal for any reason | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 10 Withdrawal due to adverse event | 2 | 105 | Risk Ratio (IV, Random, 95% CI) | 6.97 [0.88, 55.19] |
| 11 Withdrawal due to lack of efficacy | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |

### Analysis 1.1. Comparison 1 Cannabinoid versus placebo, Outcome 1 Absence of nausea.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 1 Absence of nausea

| Study or subgroup | Cannabinoid n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Chang 1979a | 2/32 | 1/32 | | 100.0 % | 2.00 [ 0.19, 20.97 ] |
| Chang 1981 | 0/16 | 0/16 | | | Not estimable |
| **Total (95% CI)** | **48** | **48** | | **100.0 %** | **2.00 [ 0.19, 20.97 ]** |

Total events: 2 (Cannabinoid), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.58 (P = 0.56)

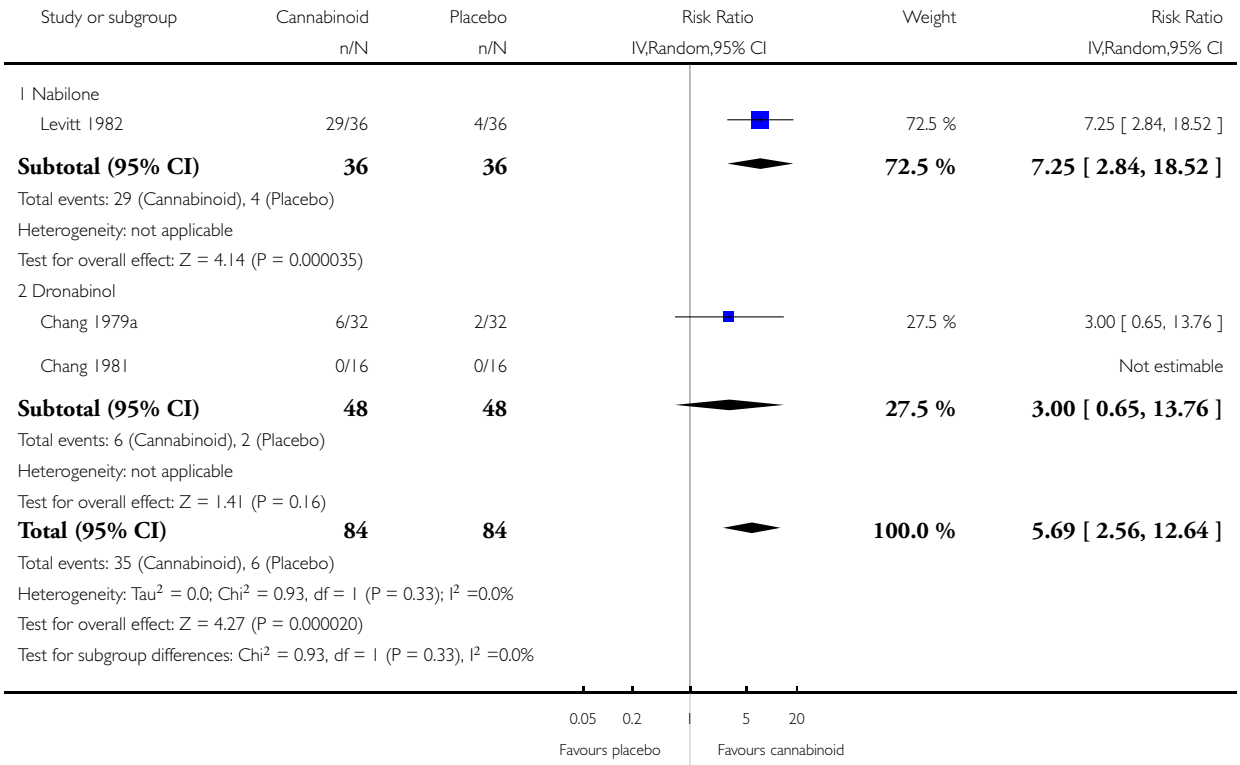
Test for subgroup differences: Not applicable

### Analysis 1.2. Comparison 1 Cannabinoid versus placebo, Outcome 2 Absence of vomiting.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 2 Absence of vomiting

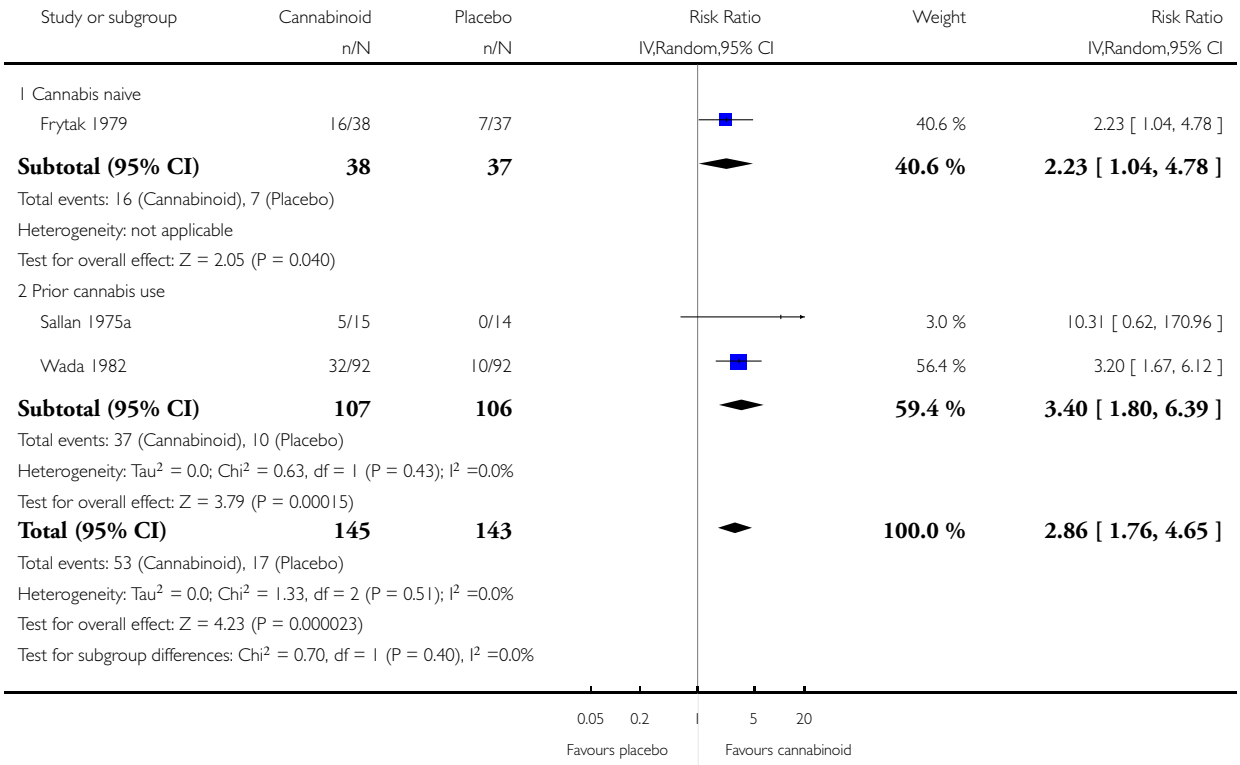


### Analysis 1.3. Comparison 1 Cannabinoid versus placebo, Outcome 3 Absence of nausea and vomiting.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 3 Absence of nausea and vomiting

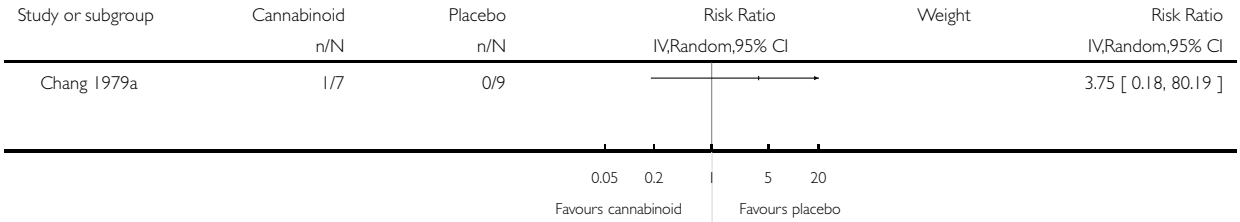


### Analysis 1.4. Comparison 1 Cannabinoid versus placebo, Outcome 4 Depression.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 4 Depression

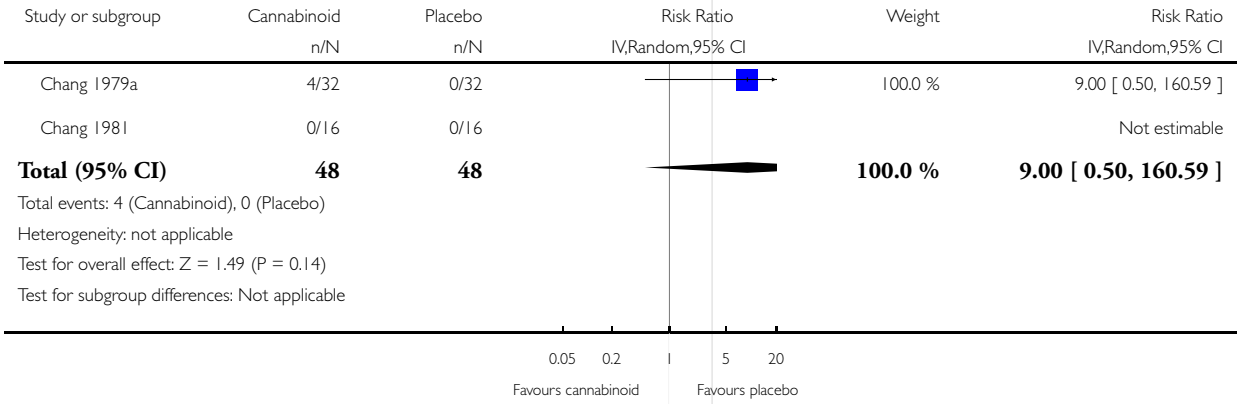



### Analysis 1.5. Comparison 1 Cannabinoid versus placebo, Outcome 5 Dysphoria.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 5 Dysphoria



### Analysis 1.6. Comparison 1 Cannabinoid versus placebo, Outcome 6 'Feeling high'.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 6 'Feeling high'

| Study or subgroup | Cannabinoid n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Chang 1981 | 14/16 | 0/16 | | 33.5 % | 29.00 [ 1.88, 448.17 ] |
| Frytak 1979 | 22/38 | 0/37 | | 32.9 % | 43.85 [ 2.76, 697.35 ] |
| Sallan 1975a | 13/16 | 0/14 | | 33.6 % | 23.82 [ 1.54, 367.46 ] |
| **Total (95% CI)** | **70** | **67** | | **100.0 %** | **31.10 [ 6.37, 151.85 ]** |

Total events: 49 (Cannabinoid), 0 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 2 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 4.25 (P = 0.000022)

Test for subgroup differences: Not applicable


### Analysis 1.7. Comparison 1 Cannabinoid versus placebo, Outcome 7 Paranoia.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 7 Paranoia

| Study or subgroup | Cannabinoid n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Chang 1979a | 1/32 | 0/32 | | | 3.00 [ 0.13, 71.00 ] |

### Analysis 1.8. Comparison 1 Cannabinoid versus placebo, Outcome 8 Sedation.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 8 Sedation

| Study or subgroup | Cannabinoid n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Chang 1979a | 12/32 | 0/32 | | 36.5 % | 25.00 [ 1.54, 405.08 ] |
| Frytak 1979 | 29/38 | 17/37 | | 63.5 % | 1.66 [ 1.12, 2.46 ] |
| **Total (95% CI)** | **70** | **69** | | **100.0 %** | **4.47 [ 0.35, 57.81 ]** |

Total events: 41 (Cannabinoid), 17 (Placebo)

Heterogeneity: $Tau^2 = 2.65$; $Chi^2 = 3.57$, df = 1 (P = 0.06); $I^2 = 72\%$

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Not applicable


### Analysis 1.9. Comparison 1 Cannabinoid versus placebo, Outcome 9 Participant preference.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 9 Participant preference

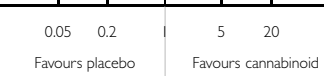
| Study or subgroup | Cannabinoid n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Levitt 1982 | 28/36 | 3/36 | | 38.2 % | 9.33 [ 3.11, 27.97 ] |
| Wada 1982 | 64/92 | 20/92 | | 61.8 % | 3.20 [ 2.12, 4.82 ] |
| **Total (95% CI)** | **128** | **128** | | **100.0 %** | **4.82 [ 1.74, 13.36 ]** |

Total events: 92 (Cannabinoid), 23 (Placebo)

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 3.21$, df = 1 (P = 0.07); $I^2 = 69\%$

Test for overall effect: Z = 3.02 (P = 0.0025)

Test for subgroup differences: Not applicable

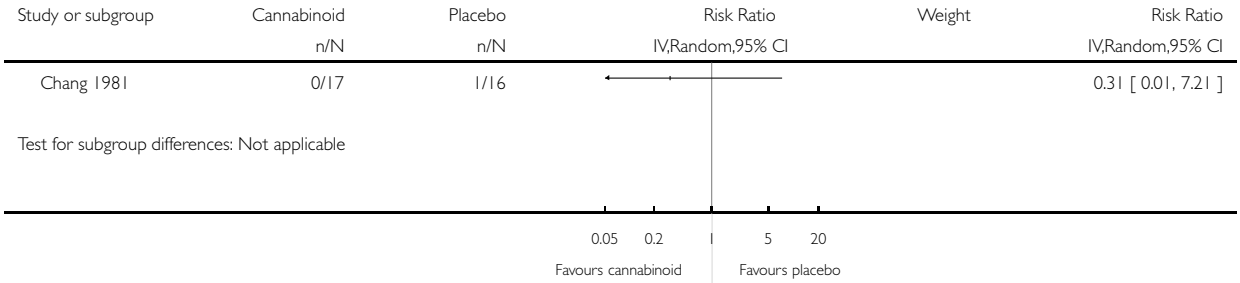


### Analysis 1.10. Comparison 1 Cannabinoid versus placebo, Outcome 10 Withdrawal for any reason.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 10 Withdrawal for any reason

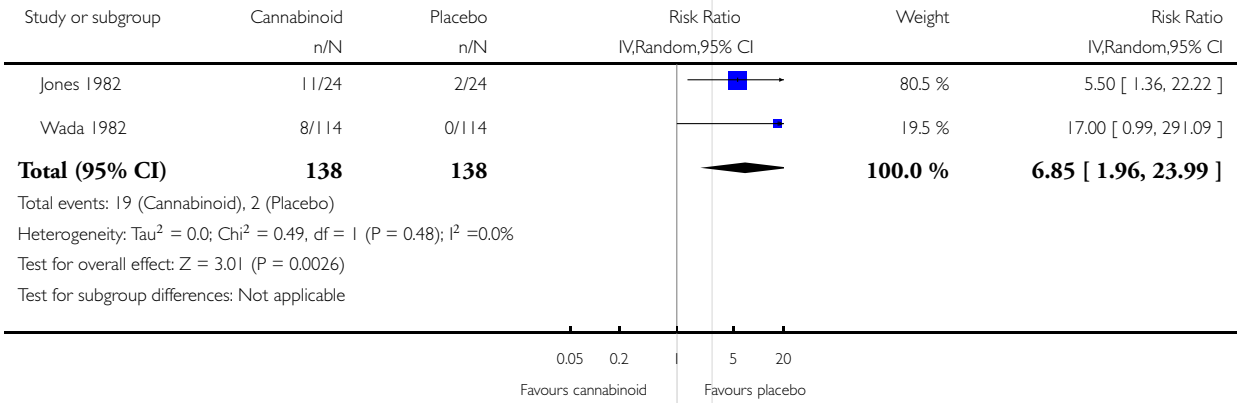



### Analysis 1.11. Comparison 1 Cannabinoid versus placebo, Outcome 11 Withdrawal due to adverse event.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 11 Withdrawal due to adverse event

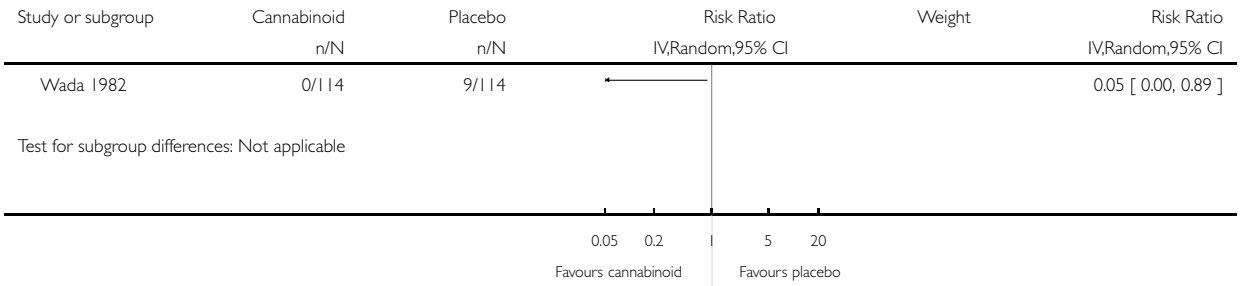


### Analysis 1.12. Comparison 1 Cannabinoid versus placebo, Outcome 12 Withdrawal due to lack of efficacy.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 1 Cannabinoid versus placebo

Outcome: 12 Withdrawal due to lack of efficacy

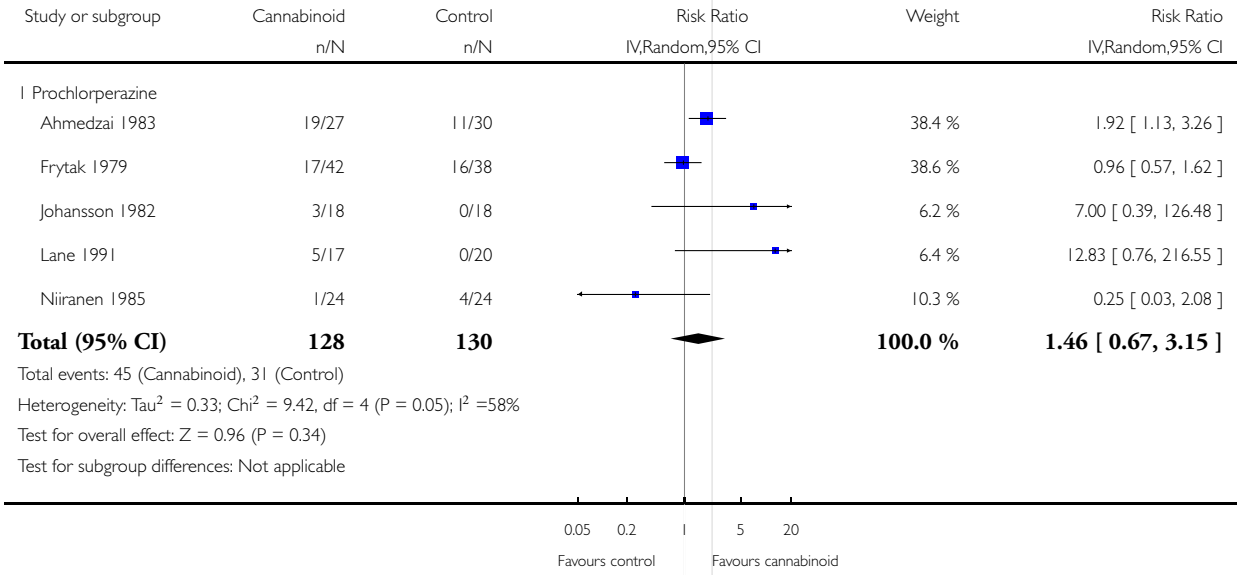



### Analysis 2.1. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 1 Absence of nausea.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 1 Absence of nausea

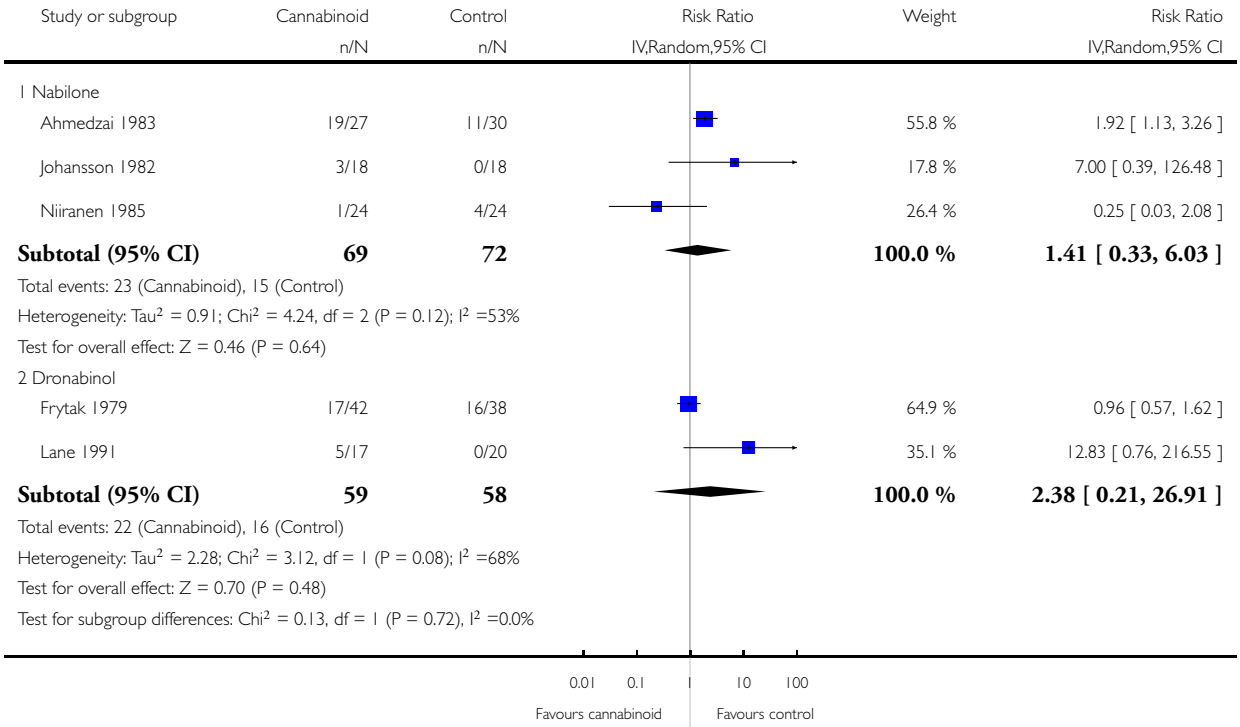


### Analysis 2.2. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 2 Absence of nausea (subgroup analysis 2).

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 2 Absence of nausea (subgroup analysis 2)



### Analysis 2.3. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 3 Absence of vomiting.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 3 Absence of vomiting

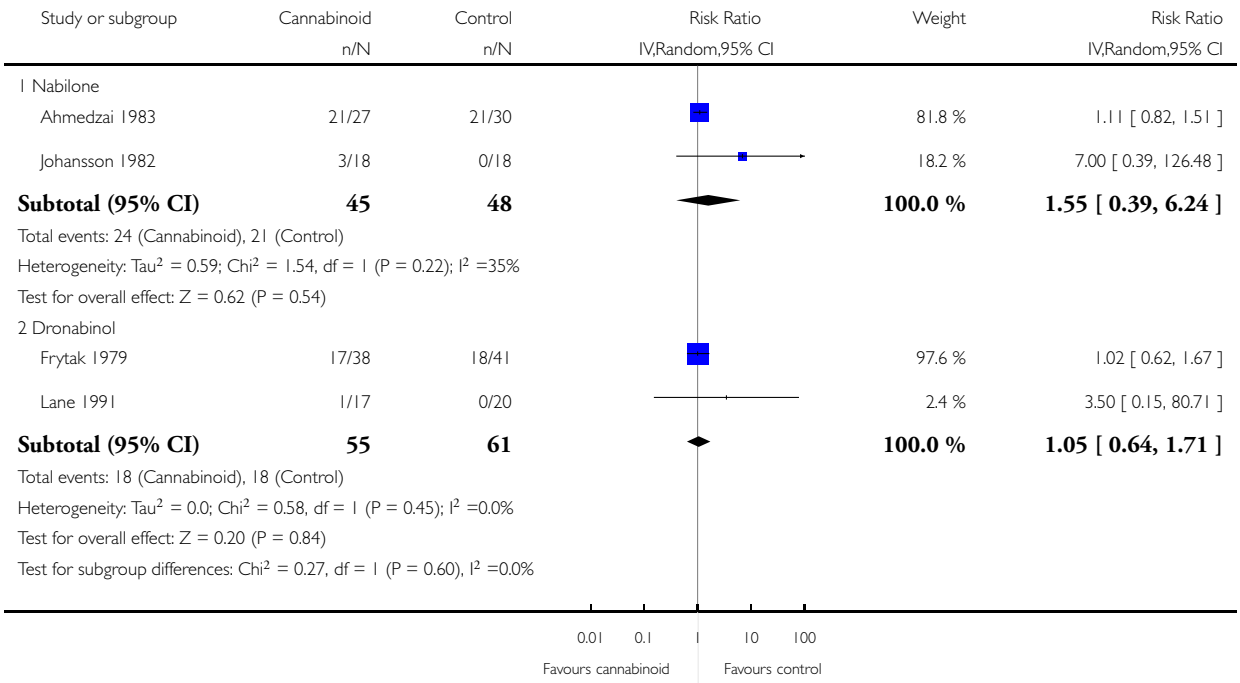
| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| 1 Prochlorperazine | | | | | |
| Ahmedzai 1983 | 21/27 | 21/30 | | 70.8 % | 1.11 [ 0.82, 1.51 ] |
| Frytak 1979 | 17/38 | 18/41 | | 27.7 % | 1.02 [ 0.62, 1.67 ] |
| Johansson 1982 | 3/18 | 0/18 | | 0.8 % | 7.00 [ 0.39, 126.48 ] |
| Lane 1991 | 1/17 | 0/20 | | 0.7 % | 3.50 [ 0.15, 80.71 ] |
| **Total (95% CI)** | **100** | **109** | | **100.0 %** | **1.11 [ 0.86, 1.44 ]** |
| Total events: 42 (Cannabinoid), 39 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.18$, df = 3 (P = 0.53); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.78 (P = 0.43) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

## Analysis 2.4. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 4 Absence of vomiting (subgroup analysis 2).

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 4 Absence of vomiting (subgroup analysis 2)



## Analysis 2.5. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 5 Absence of nausea and vomiting.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 5 Absence of nausea and vomiting

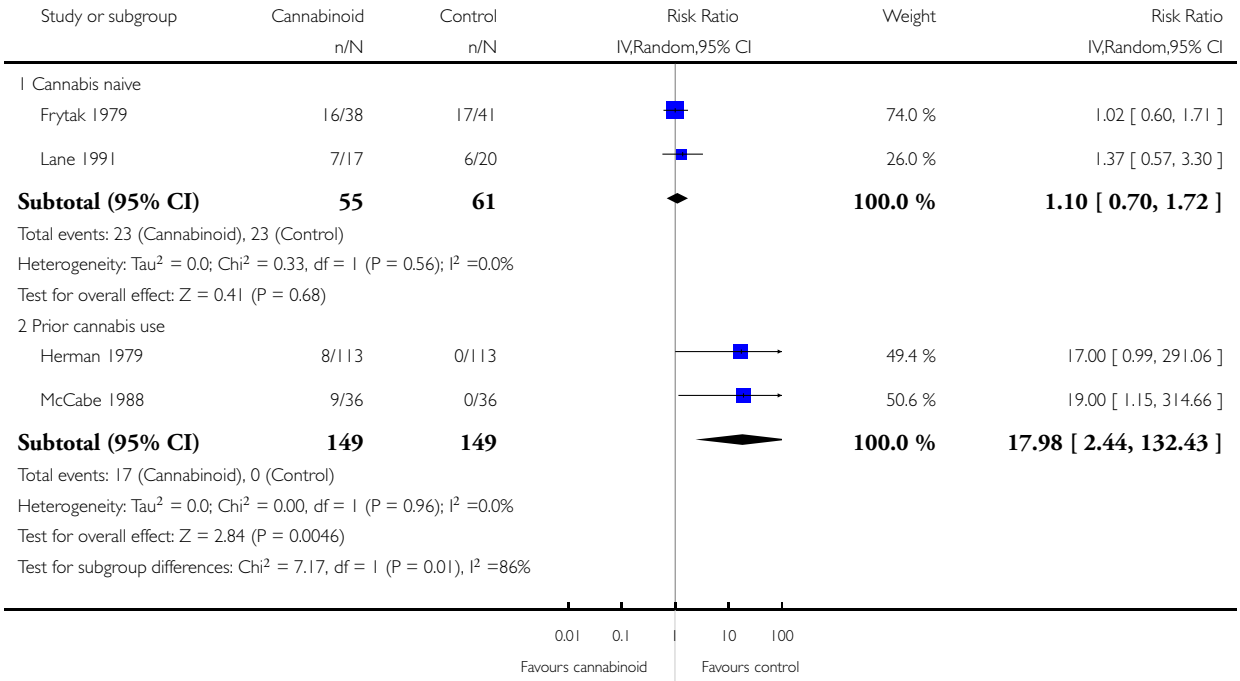
| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| 1 Prochlorperazine | | | | | |
| Frytak 1979 | 16/38 | 17/41 | | 44.2 % | 1.02 [ 0.60, 1.71 ] |
| Herman 1979 | 8/113 | 0/113 | | 9.8 % | 17.00 [ 0.99, 291.06 ] |
| Lane 1991 | 7/17 | 6/20 | | 36.1 % | 1.37 [ 0.57, 3.30 ] |
| McCabe 1988 | 9/36 | 0/36 | | 10.0 % | 19.00 [ 1.15, 314.66 ] |
| **Total (95% CI)** | **204** | **210** | | **100.0 %** | **2.00 [ 0.74, 5.38 ]** |
| Total events: 40 (Cannabinoid), 23 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 7.51$, df = 3 (P = 0.06); $I^2 = 60\%$ | | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

## Analysis 2.6. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 6 Absence of nausea and vomiting (subgroup analysis 1).

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 6 Absence of nausea and vomiting (subgroup analysis 1)

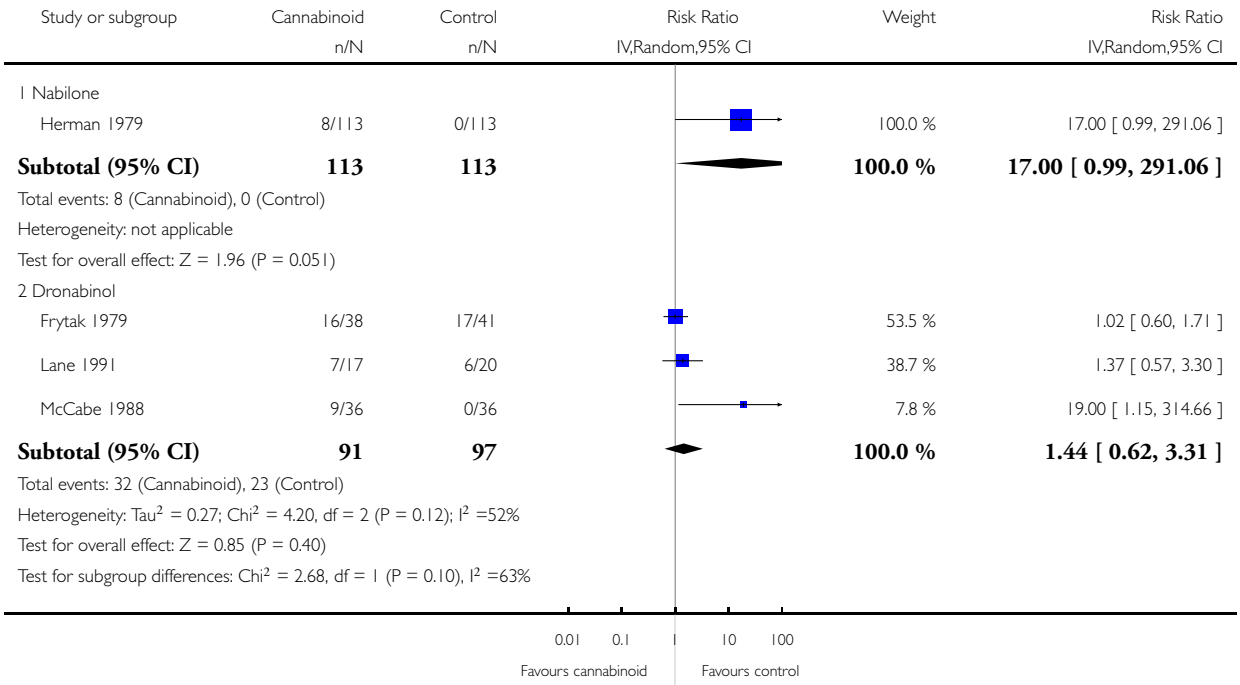


## Analysis 2.7. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 7 Absence of nausea and vomiting (subgroup analysis 2).

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 7 Absence of nausea and vomiting (subgroup analysis 2)

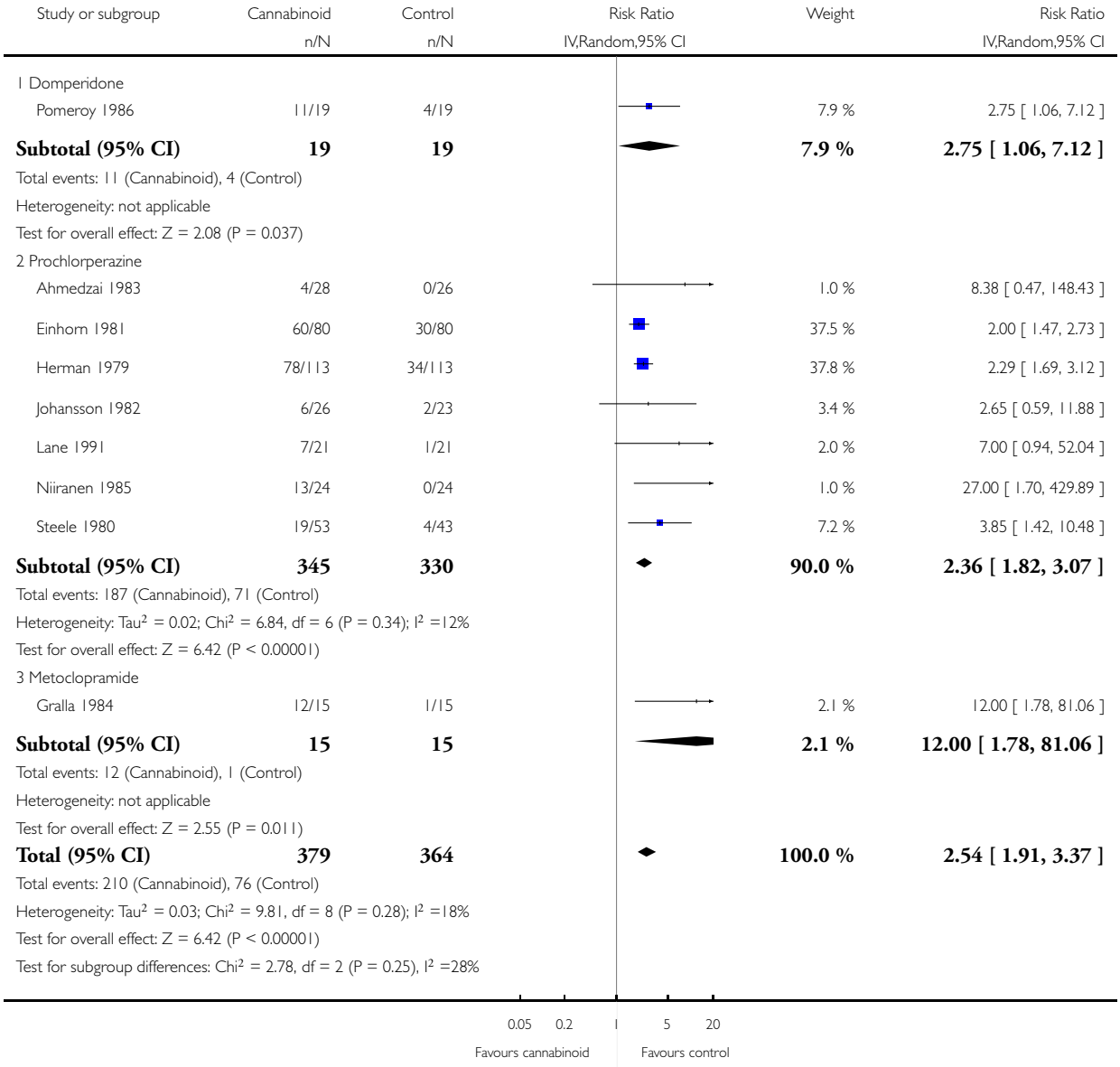


### Analysis 2.8. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 8 Dizziness.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 8 Dizziness



### Analysis 2.9. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 9 Dysphoria.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 9 Dysphoria

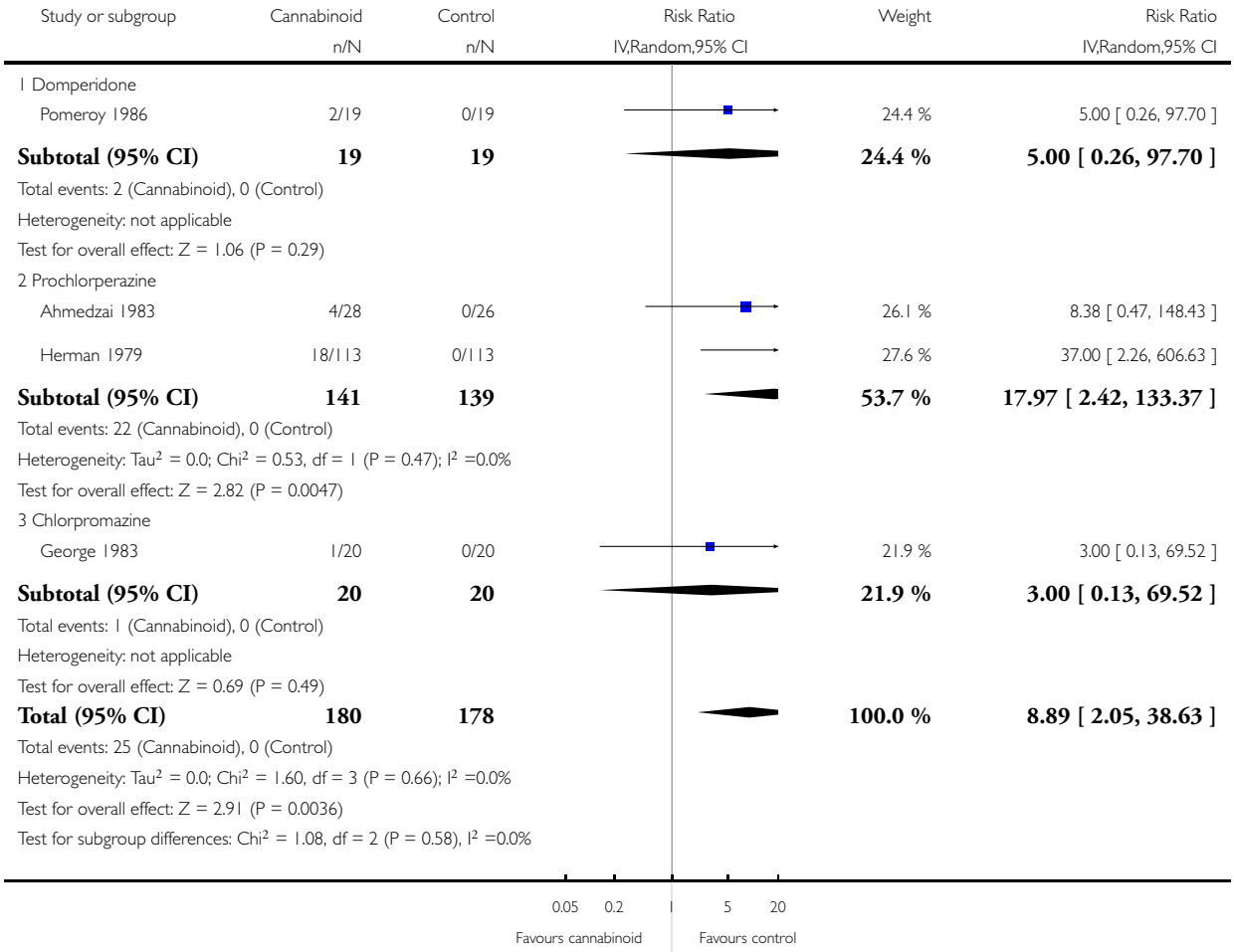
| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| 1 Prochloperazine | | | | | |
| Ahmedzai 1983 | 2/28 | 0/26 | | 31.9 % | 4.66 [ 0.23, 92.64 ] |
| Lane 1991 | 8/21 | 0/21 | | 36.6 % | 17.00 [ 1.04, 276.85 ] |
| Steele 1980 | 2/53 | 0/43 | | 31.5 % | 4.07 [ 0.20, 82.67 ] |
| **Total (95% CI)** | **102** | **90** | | **100.0 %** | **7.17 [ 1.33, 38.84 ]** |
| Total events: 12 (Cannabinoid), 0 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.58$, df = 2 (P = 0.75); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 2.29 (P = 0.022) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

### Analysis 2.10. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 10 Euphoria.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 10 Euphoria

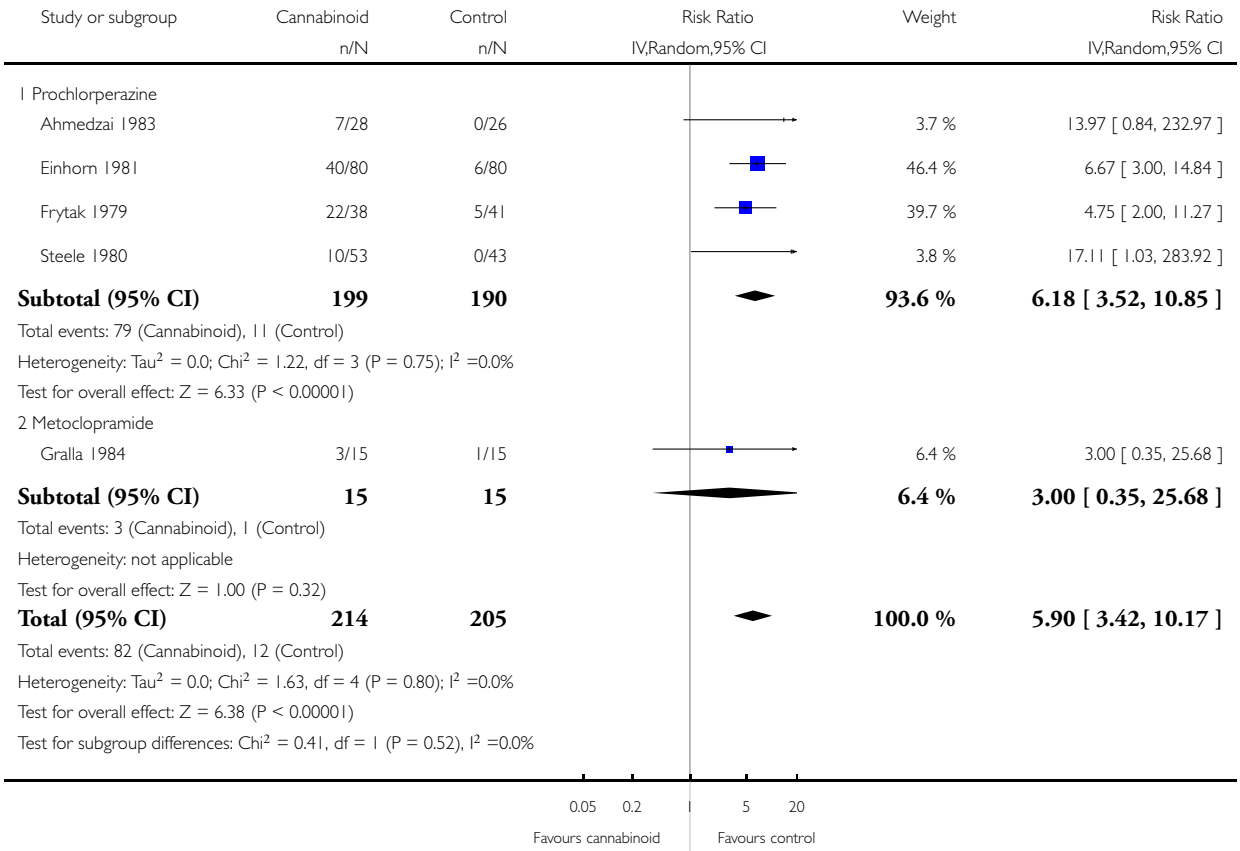


### Analysis 2.11. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 11 'Feeling high'.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 11 'Feeling high'



### Analysis 2.12. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 12 Hallucinations.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 12 Hallucinations

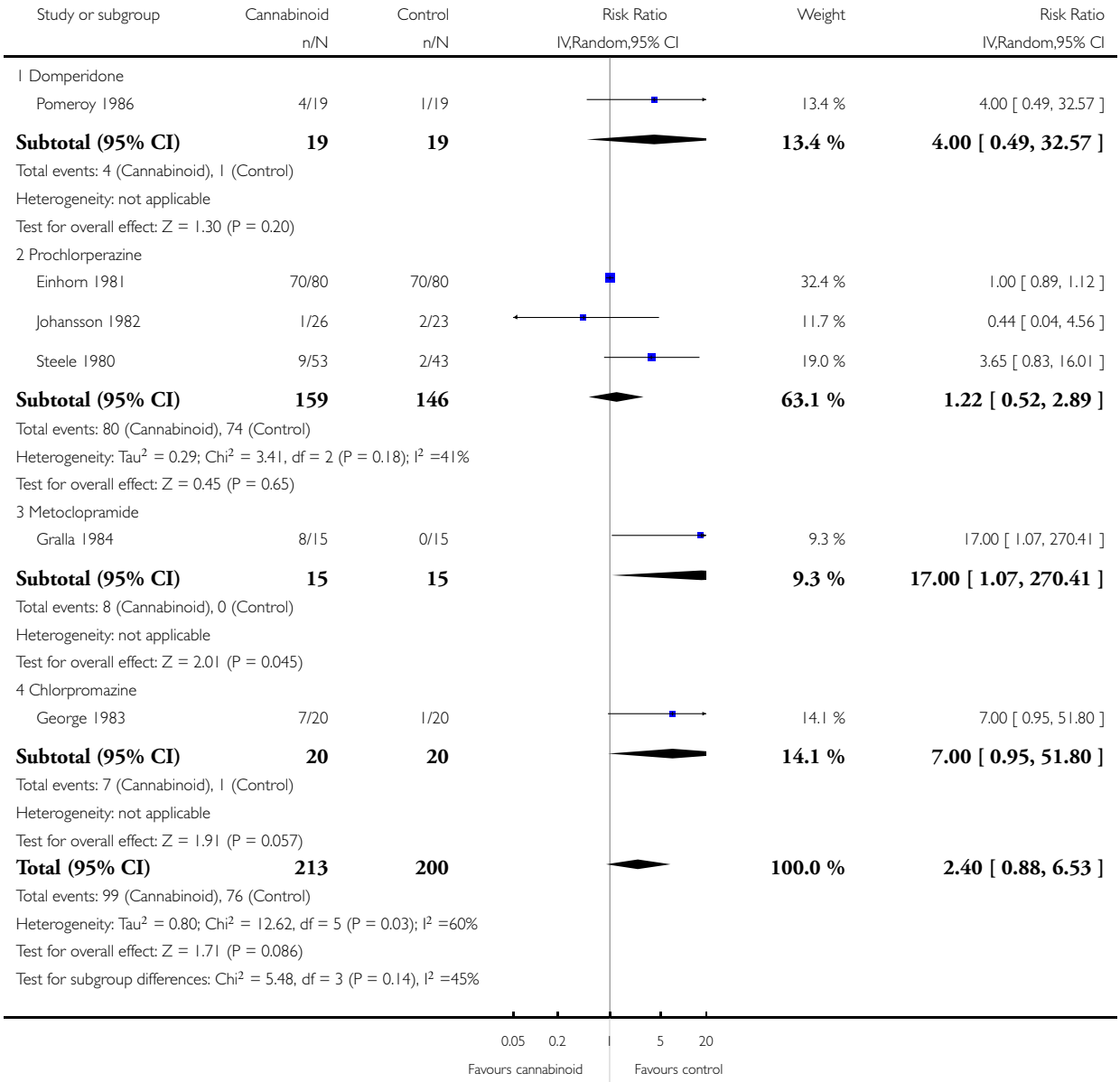
| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| 1 Prochlorperazine | | | | | |
| Niiranen 1985 | 3/24 | 0/24 | | 51.7 % | 7.00 [ 0.38, 128.61 ] |
| Steele 1980 | 2/53 | 0/43 | | 48.3 % | 4.07 [ 0.20, 82.67 ] |
| **Total (95% CI)** | **77** | **67** | | **100.0 %** | **5.39 [ 0.66, 43.68 ]** |
| Total events: 5 (Cannabinoid), 0 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 1.58 (P = 0.11) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

## Analysis 2.13. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 13 Postural hypotension.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 13 Postural hypotension

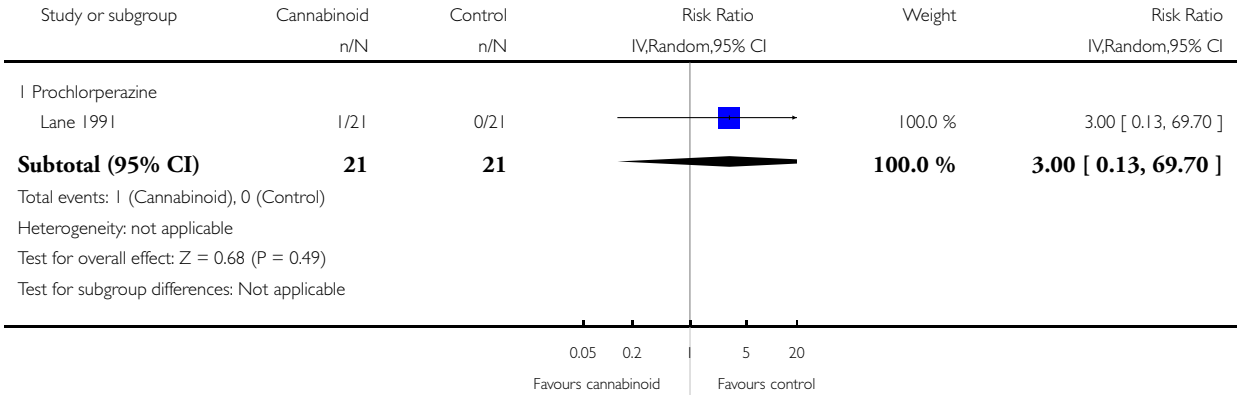


### Analysis 2.14. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 14 Paranoia.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 14 Paranoia

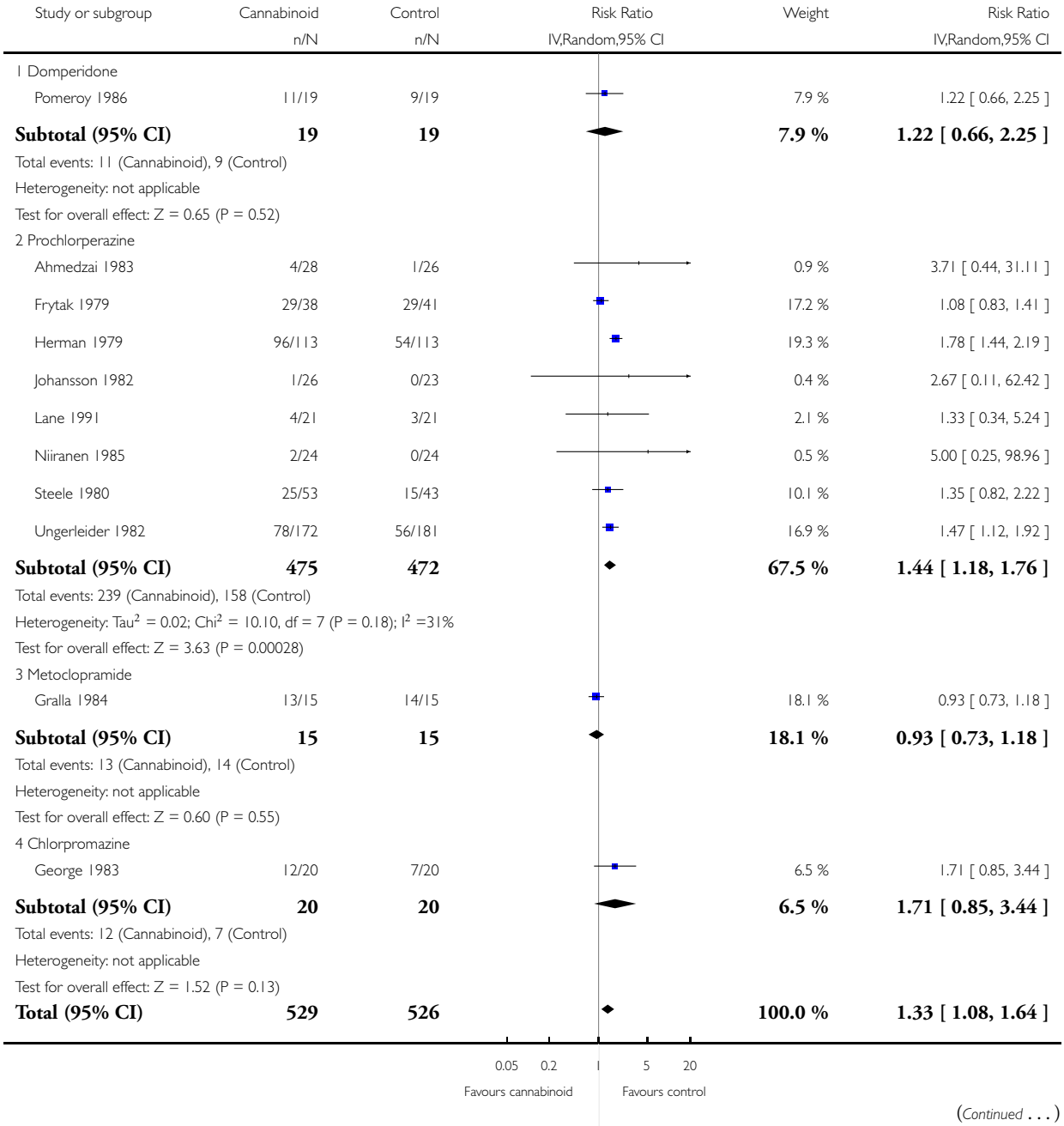


### Analysis 2.15. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 15 Sedation.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

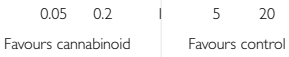
Outcome: 15 Sedation




(*Continued . . .*)

(. . . *Continued*)

| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Total events: 275 (Cannabinoid), 188 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 21.40$, df = 10 (P = 0.02); $I^2 = 53\%$ | | | | | |
| Test for overall effect: Z = 2.69 (P = 0.0071) | | | | | |
| Test for subgroup differences: $Chi^2 = 8.65$, df = 3 (P = 0.03), $I^2 = 65\%$ | | | | | |



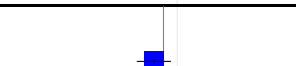

### Analysis 2.16. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 16 Depression.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 16 Depression

| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| 1 Prochlorperazine | | | | | |
| Herman 1979 | 23/113 | 30/113 | | 94.7 % | 0.77 [ 0.48, 1.23 ] |
| Johansson 1982 | 1/26 | 1/23 | | 2.9 % | 0.88 [ 0.06, 13.35 ] |
| Lane 1991 | 2/21 | 0/21 | | 2.4 % | 5.00 [ 0.25, 98.27 ] |
| **Total (95% CI)** | **160** | **157** | | **100.0 %** | **0.81 [ 0.51, 1.28 ]** |
| Total events: 26 (Cannabinoid), 31 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.49$, df = 2 (P = 0.47); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.91 (P = 0.36) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

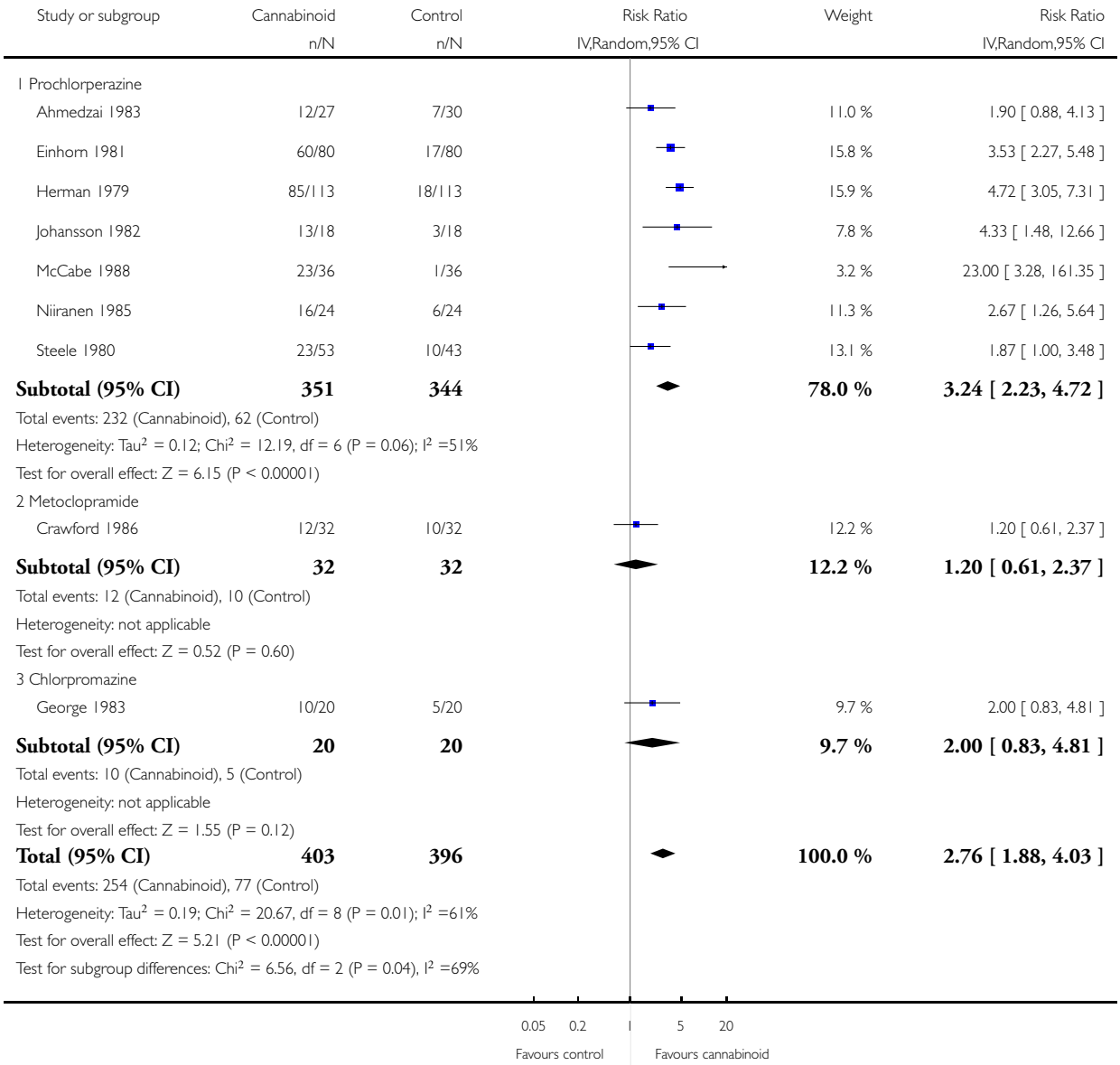


## Analysis 2.17. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 17 Participant preference.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 17 Participant preference

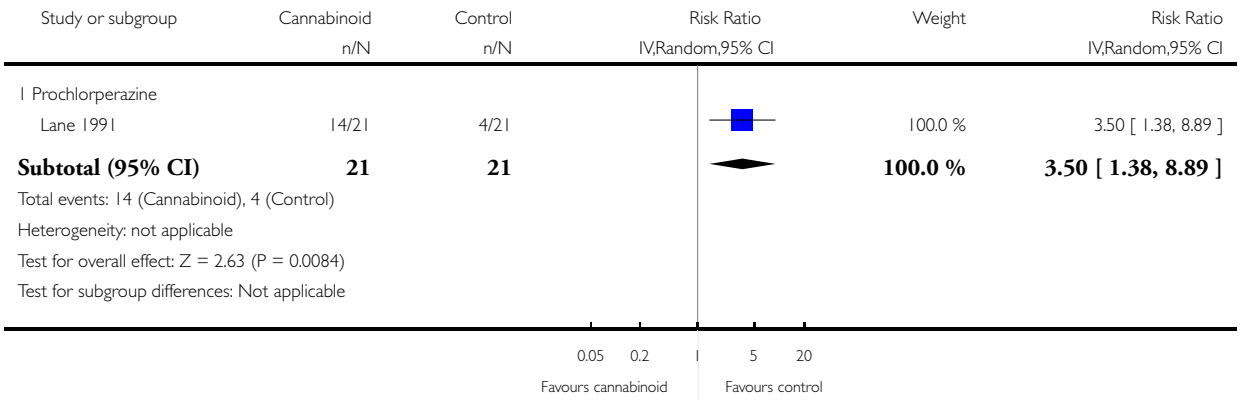


## Analysis 2.18. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 18 Withdrawal for any reason.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 18 Withdrawal for any reason

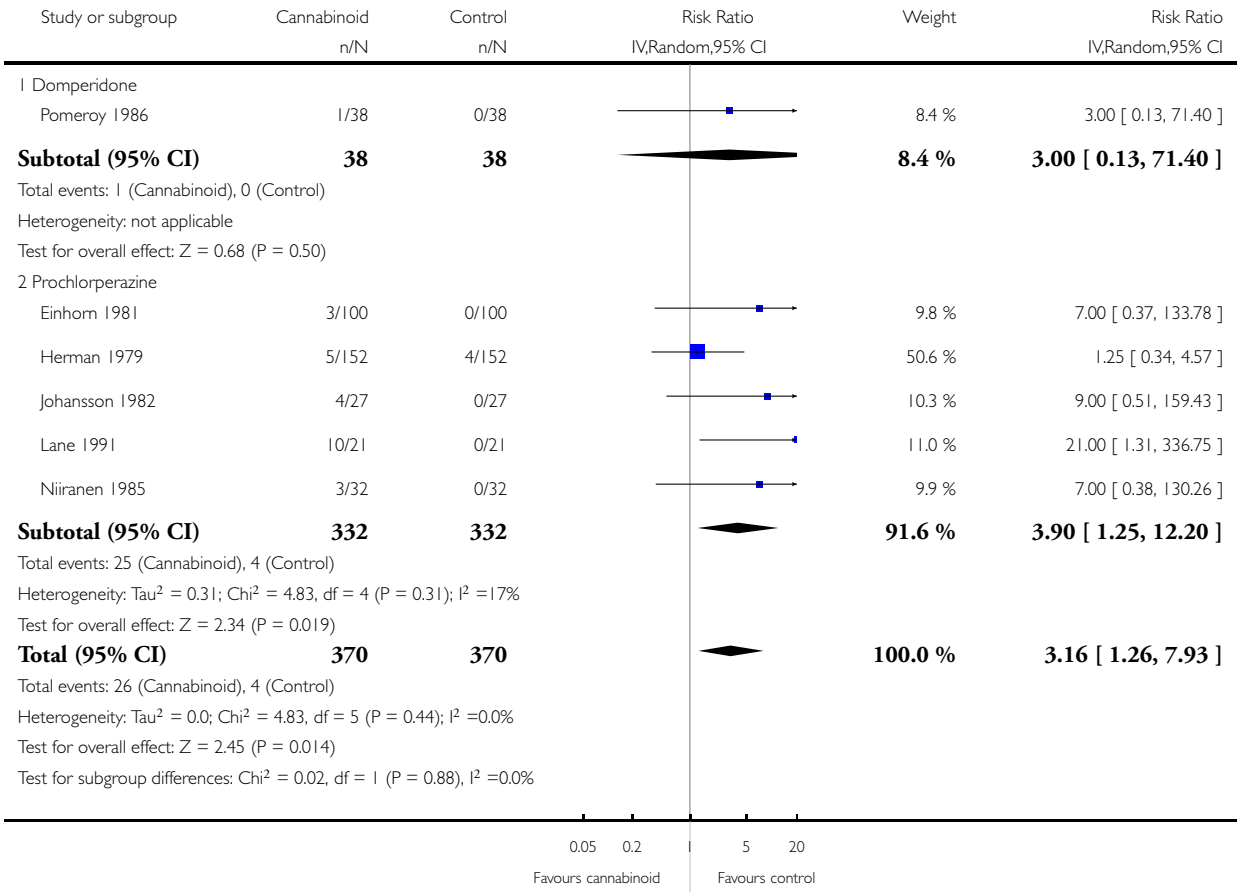


## Analysis 2.19. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 19 Withdrawal due to adverse event.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 19 Withdrawal due to adverse event

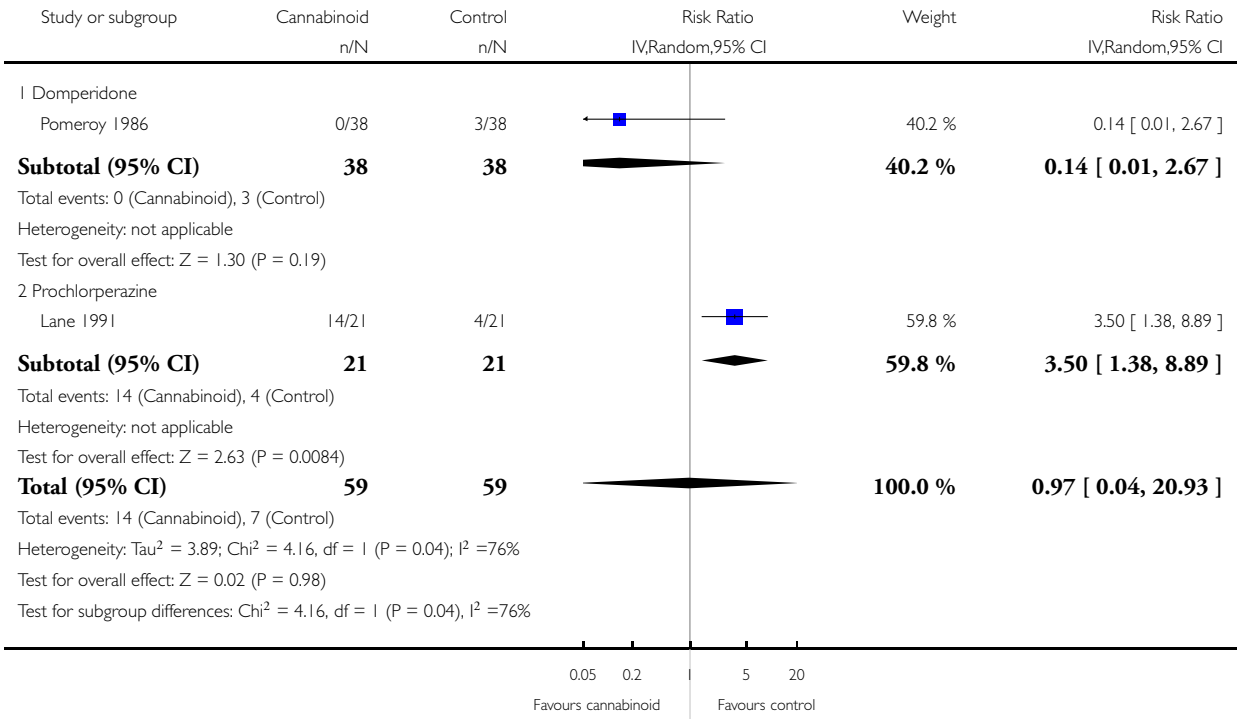


## Analysis 2.20. Comparison 2 Cannabinoid versus other anti-emetic agent, Outcome 20 Withdrawal due to lack of efficacy.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 2 Cannabinoid versus other anti-emetic agent

Outcome: 20 Withdrawal due to lack of efficacy

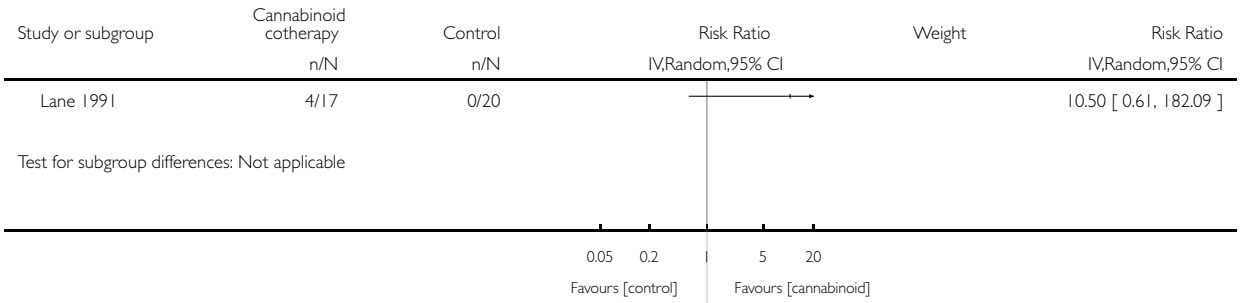


### Analysis 3.1. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 1 Absence of nausea.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 1 Absence of nausea

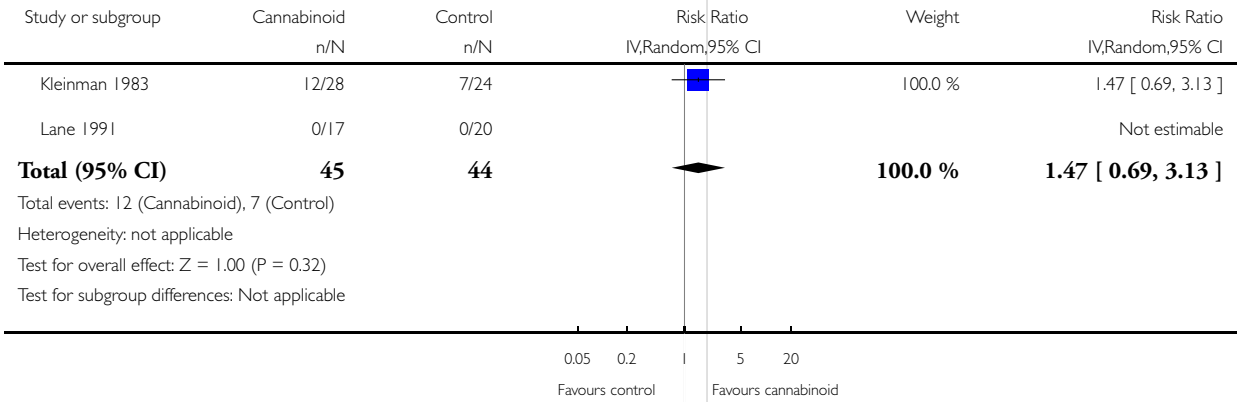



### Analysis 3.2. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 2 Absence of vomiting.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 2 Absence of vomiting



### Analysis 3.3. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 3 Absence of nausea and vomiting.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 3 Absence of nausea and vomiting

| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Lane 1991 | 8/17 | 6/20 | | | 1.57 [ 0.68, 3.63 ] |

Test for subgroup differences: Not applicable


### Analysis 3.4. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 4 Depression.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 4 Depression

| Study or subgroup | Cannabinoid n/N | Control n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Lane 1991 | 0/20 | 0/21 | | | Not estimable |

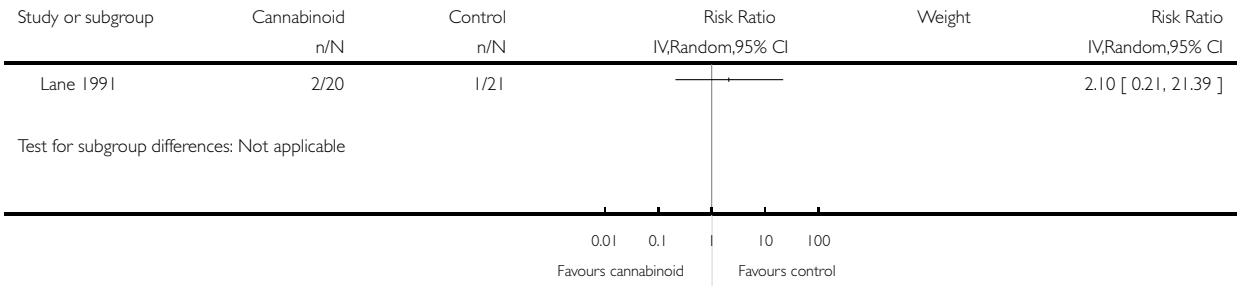
Test for subgroup differences: Not applicable

### Analysis 3.5. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 5 Dizziness.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 5 Dizziness

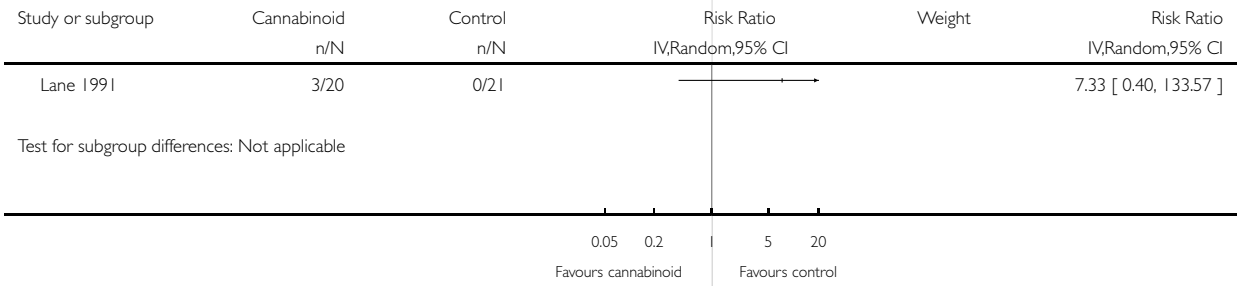



### Analysis 3.6. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 6 Dysphoria.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 6 Dysphoria

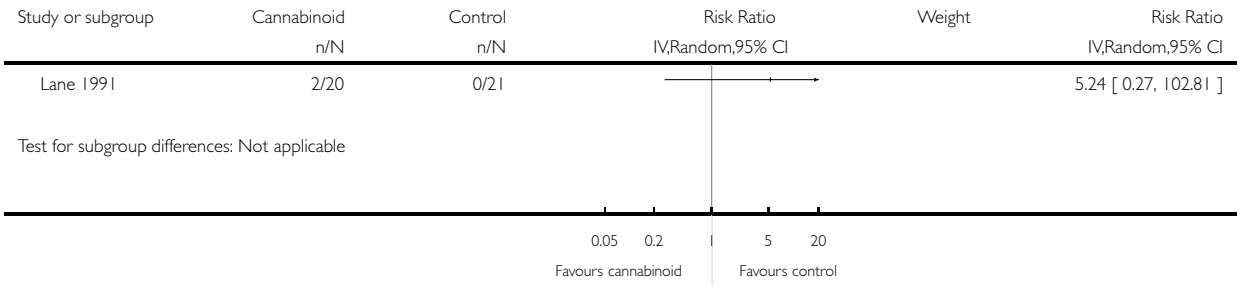


### Analysis 3.7. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 7 Paranoia.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 7 Paranoia

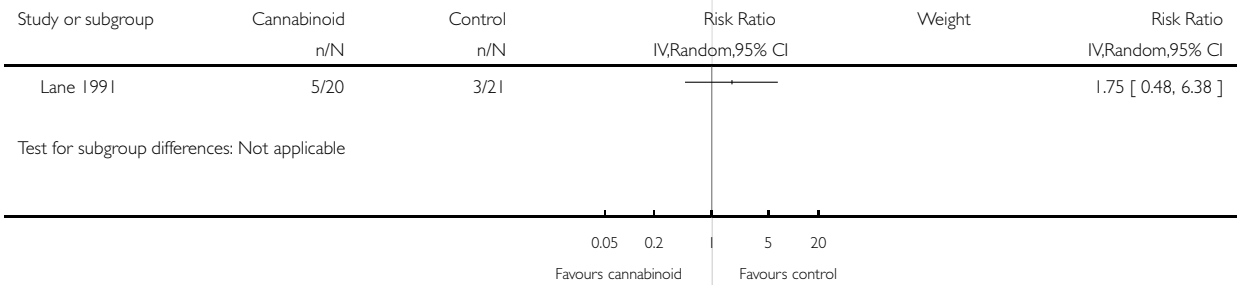



### Analysis 3.8. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 8 Sedation.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 8 Sedation

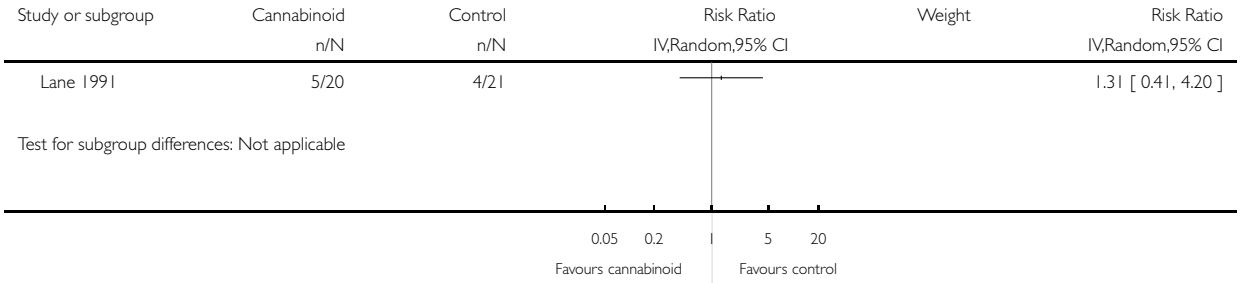


### Analysis 3.9. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 9 Withdrawal for any reason.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 9 Withdrawal for any reason

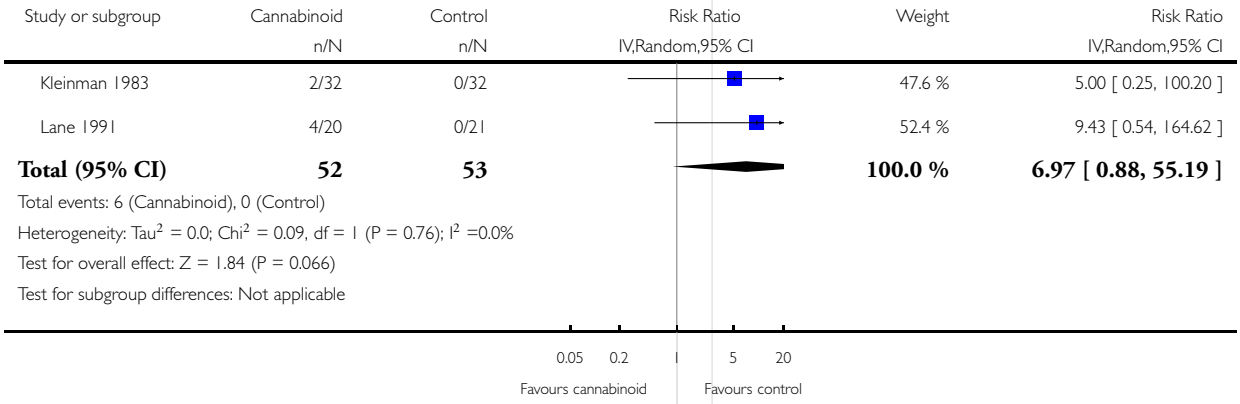



### Analysis 3.10. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 10 Withdrawal due to adverse event.

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 10 Withdrawal due to adverse event

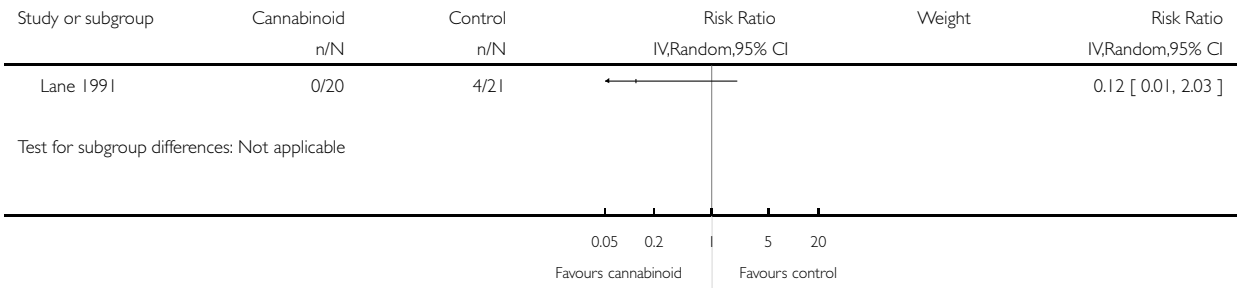


**Analysis 3.11. Comparison 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 11 Withdrawal due to lack of efficacy.**

Review: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Comparison: 3 Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome: 11 Withdrawal due to lack of efficacy




# APPENDICES

## Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Antineoplastic Agents] explode all trees
#2 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
#3 chemotherap*
#4 #1 or #2 or #3
#5 MeSH descriptor: [Nausea] explode all trees
#6 MeSH descriptor: [Vomiting] explode all trees
#7 nause* or vomit*
#8 emesis* or emetic* or antiemetic* or emetogenic*
#9 #5 or #6 or #7 or #8
#10 MeSH descriptor: [Cannabinoids] explode all trees
#11 MeSH descriptor: [Cannabis] explode all trees
#12 cannab*
#13 dronabinol
#14 nabilone
#15 tetrahydrocannabinol
#16 cesamet
#17 delta-9-THC
#18 delta-9-tetrahydrocannabinol
#19 marinol
#20 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21 #4 and #9 and #20

## Appendix 2. MEDLINE search strategy

1 exp Antineoplastic Agents/
2 exp Antineoplastic Combined Chemotherapy Protocols/
3 chemotherap*.mp.
4 1 or 2 or 3
5 exp Nausea/
6 exp Vomiting/
7 (nause* or vomit*).mp.
8 (emesis* or emetic* or antiemetic* or emetogenic*).mp.
9 5 or 6 or 7 or 8
10 exp Cannabinoids/
11 exp Cannabis/
12 cannab*.mp.
13 marinol.mp.
14 dronabinol.mp.
15 nabilone.mp.
16 tetrahydrocannabinol.mp.
17 cesamet.mp.
18 delta-9-THC.mp.
19 delta-9-tetrahydrocannabinol.mp.
20 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 randomized controlled trial.pt.
22 controlled clinial trial.pt.
23 randomized.ab.
24 placebo.ab.
25 drug therapy.fs.
26 randomly.ab.
27 trial.ab.
28 groups.ab.
29 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 4 and 9 and 20 and 29
Key: mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

## Appendix 3. EMBASE search strategy

1 exp chemotherapy/
2 exp antineoplastic agent/
3 chemotherap*.mp.
4 1 and 2 and 3
5 exp “nausea and vomiting”/
6 (nause* or vomit*).mp.
7 (emesis* or emetic* or antiemetic* or emetogenic*).mp.
8 5 or 6 or 7
9 exp cannabinoid/
10 cannabis/
11 cannab*.mp.
12 marinol.mp.
13 dronabinol.mp.
14 nabilone.mp.
15 tetrahydrocannabinol.mp.
16 cesamet.mp.

17 delta-9-THC.mp.
18 delta-9-tetrahydrocannabinol.mp.
19 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 4 and 8 and 19
21 crossover procedure/
22 double-blind procedure/
23 randomized controlled trial/
24 single-blind procedure/
25 random*.mp.
26 factorial*.mp.
27 (crossover* or cross over* or cross-over*).mp.
28 placebo*.mp.
29 (double* adj blind*).mp.
30 (singl* adj blind*).mp.
31 assign*.mp.
32 allocat*.mp.
33 volunteer*.mp.
34 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35 20 and 34
Key: [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

## Appendix 4. PsycInfo search strategy

1 antineoplastic drugs/
2 chemotherapy/
3 chemotherap*.mp.
4 1 or 2 or 3
5 nausea/
6 vomiting/
7 nause*.mp.
8 vomit*.mp.
9 (emesis or emetic* or antiemetic* or emetogenic*).mp
10 5 or 6 or 7 or 8 or 9
11 exp cannabinoids/
12 exp cannabis/
13 cannab*.mp.
14 marinol.mp.
15 dronabinol.mp.
16 nabilone.mp.
17 tetrahydrocannabinol.mp.
18 cesamet.mp.
19 delta-9-THC.mp.
20 delta-9-tetrahydrocannabinol.mp.
21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 4 and 10 and 21
key: [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

### Appendix 5. LILACS search strategy

((MH:D02.455.848.090$ OR MH:B01.650.940.800.575.100.175.500 OR cannab$ OR marinol OR dronabinol OR nabilone OR tetrahydrocannabinol OR cesamet OR delta-9-THC OR delta-9-tetrahydrocannabinol) AND (MH:nausea or MH:vomiting OR MH:emetics OR MH:antiemetics OR nausea$ OR vomit$ OR emesis OR emetic$ OR emetogenic$ OR antiemetic$) AND (MH:D27.505.954.248$ OR MH:E02.183.750.500 OR MH:E02319.077.500 OR MH:E02.319.310.037 OR chemotherap$))

## CONTRIBUTIONS OF AUTHORS

- Lesley Smith: write protocol, screened studies for inclusion, extracted and analysed data, write final review.
- Fredric Azariah: screened searches, screened studies for inclusion, extracted data, contributed to drafts of the review.
- Verna Lavender: classified chemotherapy regimens, assessed nausea and vomiting measurements, contributed to drafts of the review.
- Nicola Stoner: classified chemotherapy regimens, assessed nausea and vomiting measurements, contributed to drafts of the review.
- Silvana Bettiol: screened searches, screened studies for inclusion, extracted data, contributed to drafts of the review.

## DECLARATIONS OF INTEREST

The authors have no conflicts of interest.

## SOURCES OF SUPPORT


### Internal sources

- Cochrane, UK.

Gynaecological Cancer Review Group

### External sources

- No sources of support supplied


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Based on peer review feedback of a draft of the review and inclusion of clinical experts on the review team, we made a number of post-protocol amendments.

'Types of Participants' have changed from "*people* to "*Adults aged 18 years and over*".

We removed the plan for a subgroup analysis "*by emetic potential of the chemotherapy agent, high versus low emetogenic potentia*l" and added a new subgroup analysis "*by history of exposure to chemotherapy, chemotherapy naive versus prior chemotherapy treatment*".T

he primary outcomes we stated in the protocol are listed in the bullet points below. However, we were unable to analyse data for frequency and severity of nausea or vomiting (or both) due to use of non-valid and reliable measures, and inappropriate analysis of results reported in the primary studies. We focused on the proportion of people with cancer with complete absence of nausea or vomiting or both in common with other systematic reviews of treatments for nausea and vomiting.

- Absence of episodes of nausea and vomiting.

- Frequency of nausea and vomiting.
- Severity of nausea.

We also stated that we would only extract data for the outcome 'participant preference' for the first cross-over period only (erroneously), and, due to none of the trials reporting this, we extracted responses for the entire study period.

We added three additional adverse effects as secondary outcomes: focal dystonia, extrapyramidal effects and oculogyric crisis.

We did not contact pharmaceutical companies for data on file.

## Methods for future updates

### Data extraction and management

For continuous outcomes (severity of nausea measured using a validated symptom scale), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed in each treatment arm at the end of follow-up in order to estimate the mean difference between treatment arms (or standardised mean difference if measured on different scales) and its standard error.

Data for frequency of nausea or vomiting, or both, may be reported in a number of ways. For data presented as counts (number of nausea or vomiting (or both) episodes), we will extract the number of events and person-time at risk, if presented, in order to calculate a nausea and vomiting rate per treatment group. For data presented as continuous data, we will extract the mean number of events (nausea or vomiting (or both) episodes) in each treatment group. For data presented as categorical data (number of participants who experience at least five events), we will proceed as described above for dichotomous data.

### Data collection and analysis

If the results are statistically significant, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) or additional harmful outcome (NNTH). For continuous outcomes, we will calculate the difference in means between treatment arms at the end of follow-up. We will consider the magnitude of the effect of an intervention as at least moderate if the 'effect size' is superior to 0.5 (Cohen 1988). For outcomes reported as rates, we will calculate the rate ratio.

Wherever the data are missing or only imputed data are reported, we will contact the trial authors and request the data on the outcomes only among the participants who were assessed.

Where the trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups and treat comparisons between each treatment group and the split comparison group as independent comparisons.

#### Unit of analysis

In future updates it may be possible to:

- obtain data from study authors for each treatment period or summary statistics of the degree of agreement between each person's responses, or both;
- adjust the analyses for the dichotomous outcomes to take into account the paired data.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antiemetics [adverse effects; *therapeutic use]; Antineoplastic Agents [adverse effects]; Cannabinoids [adverse effects; *therapeutic use]; Chlorpromazine [adverse effects; therapeutic use]; Dizziness [chemically induced]; Domperidone [adverse effects; therapeutic use]; Euphoria; Metoclopramide [adverse effects; therapeutic use]; Nausea [chemically induced; *drug therapy]; Neoplasms [*drug therapy]; Prochlorperazine [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Vomiting [chemically induced; *drug therapy]

### MeSH check words

Adult; Humans

# REFERENCE #15

Published in final edited form as:
*Eur J Pharmacol*. 2014 January 5; 722: . doi:10.1016/j.ejphar.2013.09.068.

# Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system

**Keith A. Sharkey**[1,*], **Nissar A. Darmani**[2], and **Linda A. Parker**[3]

[1]Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, Canada

[2]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, California, USA

[3]Department of Psychology, University of Guelph, Guelph, Ontario, Canada

## Abstract

Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions.

### Keywords

Cannabis; serotonin; emesis; brainstem; insular cortex; $CB_1$ receptor; $CB_2$ receptor

## 1. Introduction

Reflex mechanisms that serve to protect a host from injury and disability represent important and frequently well-conserved adaptations to a hostile external environment. Rarely do these adaptations, such as blinking or sneezing, become “hijacked” by physiological or pathophysiological processes in the body, not involving the organ they evolved to protect. Unfortunately, that is not the case for nausea and vomiting. Nausea is an aversive experience that often precedes emesis (vomiting), but is distinct from it (Borison and Wang, 1953; Carpenter, 1990; Horn, 2008; Andrews and Horn, 2006; Stern et al., 2011). Retching and vomiting lead to the forceful expulsion of gastric and/or upper intestinal contents, the



[*]Author for Correspondence: Dr. Keith Sharkey, Department of Physiology and Pharmacology, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada, Tel: 403-220-4601, Fax: 403-283-2700, ksharkey@ucalgary.ca.

primary function of which is to remove ingested materials or food that may be contaminated or potentially harmful. Nausea associated with emesis serves as an unconditioned stimulus for learning and memory; food that becomes associated with nausea and vomiting will be avoided in future encounters (Borison and Wang, 1953; Carpenter, 1990; Horn, 2008; Andrews and Horn, 2006; Stern et al., 2011).

In the natural environment, as a protective reflex, nausea and vomiting are very important adaptations found in most vertebrate species (Borison et al., 1981). However, possibly because of its importance, the sensitivity of this reflex is very low, making it easily activated. In various disease states, e.g. diabetes and labyrinthitis (Koch, 1999; Schmäl, 2013), the inappropriate activation of this reflex leads to severe and debilitating symptoms. Many central nervous system conditions, including elevated intracranial pressure, migraine headache and concussion also cause nausea and vomiting (Edvinsson et al., 2012; Mott et al, 2012; Stern et al., 2011). Nausea and vomiting are frequent, unwanted, side-effects of a range of medications used to treat a variety of conditions, notably cancer chemotherapeutic agents (Hesketh, 2005; Rojas and Slusher, 2012). Pregnancy-induced nausea and vomiting are reportedly adaptive mechanisms, but hyperemesis gravidarum can severely compromise both the health of the mother and the developing fetus (Patil et al, 2012; Sanu and Lamont, 2011; Sherman and Flaxman, 2002). Finally, motion sickness, which results from a sensory conflict between visual and vestibular stimuli, can be of immense discomfort, and severely limit certain activities (Schmäl, 2013; Yates et al., 1998). Nausea and vomiting are significant in our society and understanding them represents both an important goal and a major challenge; the former because of the substantial health implications, but the latter because it is hard to judge if an experimental animal is nauseated and commonly used laboratory animals are some of the few species that do not vomit! Nevertheless, significant progress has been made in our understanding of the processes of nausea and vomiting, which has led to new and improved pharmacological treatments for these disorders in the last 20–30 years, as described in many of the accompanying articles in this volume and previous reviews (Rojas and Slusher, 2012; Sanger and Andrews, 2006; Schmäl, 2013).

One of the oldest pharmacological remedies for nausea and vomiting is the plant cannabis (Kalant, 2001). In clinical trials, cannabis-based medicines have been found to be effective anti-emetics and even surpass some modern treatments in their potential to alleviate nausea (Cotter, 2009; Tramèr et al., 2001). However, it was not until the early 1990s that the mechanism of action of cannabis was established following the cloning of the “cannabinoid” (CB) receptors (Howlett et al., 2002; Pertwee et al., 2010). The significance of this discovery was enhanced when it was realized that these receptors were part of an endogenous cannabinoid (endocannabinoid) system in the brain and elsewhere in the body (Di Marzo and De Petrocellis, 2012; Izzo and Sharkey, 2010; Mechoulam and Parker 2013; Piomelli, 2003). The endocannabinoid system serves to modulate the expression of nausea and vomiting when activated by central or peripheral emetic stimuli (Darmani and Chebolu, 2013; Parker et al., 2011).

In this article we will outline the endocannabinoid system and then describe what is known about this system in relation to the neural circuits of nausea and vomiting. We will describe recent findings on the anti-emetic effects of cannabinoids and show how manipulation of elements of the endocannabinoid system can modify the expression of emesis. We will discuss at some length the evidence that cannabinoids and the endocannabinoid system can regulate nausea, because this is an area that has been not been considered so fully in the past. We will then briefly describe the paradoxical effect of chronic exposure to high doses of cannabis that in some people causes a cyclic vomiting syndrome. Finally, we will conclude with some future directions for this research by identifying gaps in our knowledge of the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system.

## 2. The endocannabinoid system

The isolation of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) as the major psychoactive ingredient in cannabis was an important milestone in neuropharmacology (Howlett et al., 2002; Pertwee et al., 2010). This discovery provided the impetus for extensive investigations that led to an understanding of many of the central and peripheral sites of action of cannabis and ultimately to the cloning of the two G-protein coupled cannabinoid receptors; $CB_1$ and $CB_2$. $CB_1$ receptors are distributed throughout the central and peripheral nervous system, but also in many other sites throughout the body (Howlett et al., 2002; Pertwee et al., 2010). In the brain they are frequently expressed in high density on presynaptic nerve terminals of both inhibitory and excitatory nerves, depending on the region (Katona and Freund, 2012). $CB_2$ receptors are expressed on cells and organs of the immune system, but they are also found in the brain and at other sites in the body (Onaivi et al., 2012; Pacher and Mechoulam, 2011). The actions of cannabinoids can largely be accounted for by these two receptors, however, there are some well-described non-cannabinoid$_1$-, non-$CB_2$ receptor-mediated actions of cannabinoids. To date there is limited evidence for a third cannabinoid receptor, though some cannabinoids act at the GPR55 receptor (Pertwee et al., 2010). Whether GPR55 has any role in nausea and vomiting is not known and has not been examined to date.

Both cannabinoid receptors signal through $G_{i/o}$ proteins, inhibiting adenylyl cyclase and activating mitogen-activated protein kinase. Activation of the cannabinoid receptors limits calcium entry into cells by inhibiting N- and P/Q-type calcium currents and further inhibits cellular excitability by activating A-type and inwardly rectifying potassium channels (Howlett et al., 2002; Pertwee et al., 2010).

Shortly after the discovery of the $CB_1$ receptor, two endogenous cannabinoid receptor ligands, *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were isolated (Di Marzo and De Petrocellis, 2012). Unlike many preformed intercellular mediators, endocannabinoids are made on demand when cells are stimulated with either an increase in intracellular calcium (Alger and Kim, 2011), or following metabotropic receptor activation involving $G_{q/11}$ or possibly $G_s$ proteins (Gyombolai et al., 2012). These ligands are found in the brain and in the periphery, for example, in the gastrointestinal tract (Izzo and Sharkey, 2010), where they act at cannabinoid and other receptors (see below).

Both endocannabinoids are made by enzymatic pathways that have specific localization patterns in the brain that give important clues to their functional roles. Best characterized are the biosynthetic and degradative pathways for the formation and hydrolysis of 2-AG (Blankman and Cravatt, 2013; Long and Cravatt, 2011; Ueda et al., 2010, 2011). The most important pathway for the synthesis of 2-AG begins with activation of a phosphoinositol (PI)-phospholipase C (PLC) which hydrolyzes inositol phospholipids at the *sn-2* position producing diacylglycerol (DAG). The hydrolysis of DAG via *sn*-1-selective diacylglycerol lipases (DAGL)-α and DAGL-β then leads to the formation of 2-AG. Alternatively, but less well characterized, is the sequential hydrolysis of PI by phospholipase $A_1$ to make lyso-PI which is then further hydrolysed to 2-AG by lyso PI-specific PLC. In the brain, endocannabinoid signaling is abolished in DAGL-$\alpha^{-/-}$ mice (Gao et al., 2010), suggesting this form of the enzyme is the key physiological rate limiting enzyme for 2-AG biosynthesis. The metabolism of 2-AG is complex and potentially can involve enzymatic oxygenation, acylation, or phosphorylation; but probably the most important pathway for 2-AG metabolism is hydrolysis (Blankman and Cravatt, 2013; Ueda et al., 2011). Using a functional proteomic approach, Blankman *et al.* (2007) showed that the majority (~85%) of the 2-AG hydrolyzing activity in the brain was due to the serine hydrolase, monoacylglycerol lipase (MAGL) (Dinh et al., 2002). The remaining hydrolytic activity was due to the enzymes α/β-hydrolase domain-containing protein-6 (ABHD-6) and ABHD-12

(Marrs et al., 2010; Savinainen et al., 2012). MAGL is located presynaptically (Gulyas et al., 2004), but ABHD6 is found in postsynaptic sites (Marrs et al., 2010), suggesting their roles in the regulation of 2-AG are distinct, and possibly important for the establishment of different pools of 2-AG in cellular compartments in the brain. The distribution of these enzymes elsewhere in the body is not well understood.

The major biosynthetic enzyme for the formation of 2-AG in the brain, DAGL-α, was identified in the plasma membranes of postsynaptic dendritic spines in various brain regions (Yoshida et al., 2006). In contrast, as noted above, $CB_1$ receptors are located presynaptically. This anatomical arrangement is entirely consistent with 2-AG being a retrograde synaptic neurotransmitter in the CNS: being synthesized and released from a postsynaptic site and acting to limit neurotransmitter release from presynaptic terminals via $CB_1$ receptor activation, and then having its action terminated by hydrolysis (Alger and Kim, 2011; Castillo et al., 2012). There is some evidence for a basal pool of 2-AG in neurons, since DAGL inhibitors do not block all the synaptic endocannabinoid signaling in some situations, whereas endocannabinoid signaling is completely blocked in $DAGL^{-/-}$ mice (Min et al., 2010). However, the significance of this observation remains to be determined.

Anandamide is the other major endocannabinoid ligand. Anandamide acts not only at $CB_1$ receptors but strong evidence supports the idea that it is also an “endovanilloid”, acting on the ligand-gated transient receptor potential (TRP) vanilloid 1 receptor, and possibly other TRP receptor ion channels (Di Marzo and De Petrocellis, 2012). It should be noted that both anandamide and 2-AG might also be natural ligands for receptors other than the cannabinoid receptors, as data is accumulating that they can modulate receptor binding at a variety of receptors including the G protein-coupled muscarinic cholinergic and mu opioid receptors, nuclear peroxisome proliferator-activated receptors and ligand-gated ion channels such as the $5\text{-}HT_3$ receptor, albeit with relatively low potency and/or efficacy in many cases (Pertwee et al., 2010).

An important route of anandamide synthesis begins with the membrane phospholipid precursor, N-arachidonoylphosphatidylethanolamine (NAPE), which is formed by the transfer of arachidonic acid from the *sn*-1 position of a donor phospholipid to phosphatidylethanolamine by N–acyltransferase. Hydrolysis of NAPE by an N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) produces anandamide (Blankman and Cravatt, 2013; Di Marzo and De Petrocellis, 2012; Ueda et al., 2010). That said, the levels of anandamide in $NAPE\text{-}PLD^{-/-}$ mice are very similar to those of wild type animals and the increase in anandamide seen in the brain after blocking its degradation *in vivo* is also similar, suggesting that another biosynthetic pathway can completely compensate for the NAPE-PLD pathway or that there are at least two parallel pathways for anandamide synthesis in the brain (Leung et al., 2006). These additional enzymatic pathways for the production of anandamide include the sequential deacylation of NAPE by the enzyme alpha beta-hydrolase 4 and the cleavage of glycerophosphate to yield anandamide, and a PLC-mediated hydrolysis of NAPE which produces phosphoanandamide, which is then dephosphorylated to produce anandamide (Blankman and Cravatt, 2013; Di Marzo and De Petrocellis, 2012; Liu et al., 2006, 2008; Ueda et al., 2010). Little is known about the distribution of these additional biosynthetic enzymatic pathways in the brain, but the distribution of NAPE-PLD has recently been described.

NAPE-PLD has been localized in many regions of the brain, and its distribution is similar to the distribution of the $CB_1$ receptor, but unlike DAGL-α, it has been localized in both pre- and post-synaptic structures (Egertová et al., 2008). Furthermore, it appears to be localized intracellularly on organelles including the smooth endoplasmic reticulum, suggesting that

anandamide may act as both an anterograde signaling molecule and/or as an intracellular regulator. Since the binding site for anandamide on TRPV1 receptors is intracellular (Di Marzo and De Petrocellis, 2012), and anandamide is a full agonist of TRPV1 (whereas it is only a partial agonist at the $CB_1$ receptor; Howlett et al., 2002; Pertwee et al., 2010) it seems possible that its primary function in the brain may be distinctly different from that of the synaptic retrograde signaling function of 2-AG (Alger and Kim, 2011; Castillo et al., 2012). In support of this idea, anandamide has been shown to be released tonically in the hippocampus and seems to be responsible for regulating inhibitory network activity in a homeostatic manner (Kim and Alger, 2010). In this case, its actions appear to be retrograde in nature, and so given the distribution of NAPE-PLD noted above, perhaps this is not the source of the anandamide, which has still to be resolved. Much more work is needed to establish the enzyme systems responsible for the production of endocannabinoids in specific brain regions. But as we will see later, both $CB_1$ and TRPV1 receptors are responsible for the antiemetic actions of the endocannabinoid anandamide and the related compound N-arachidonoyl-dopamine (Sharkey et al., 2007).

The principal enzyme for the degradation of anandamide is fatty acid amide hydrolase (FAAH). FAAH is found in neurons throughout the brain, where its postsynaptic distribution is consistent with the idea that the function of anandamide may be primarily to mediate anterograde or intracellular signaling (Gulyas et al., 2004; Tsou et al., 1998). A surprising finding is that levels of anandamide are not only regulated by FAAH, but are reduced in DAGL-$\alpha^{-/-}$ mice, pointing to a convergence in endocannabinoid signaling pathways where 2-AG production regulates the levels of anandamide (Gao et al., 2010). Exactly how this is occurs is not known. Convergence of endocannabinoid signaling was also revealed using dual FAAH and MAGL inhibitors and MAGL inhibitors in $FAAH^{-/-}$ mice (Long et al., 2009; Wise et al., 2012). These studies suggest there is significant cross-talk between these ligand systems and the cannabinoid receptors.

In summary, the endocannabinoid system is responsible for shaping and refining synaptic signaling in the brain and the peripheral nervous system. There is considerable complexity to this system and in only a few areas have systematic studies of all of its many components been conducted. To date, the endocannabinoid system in the peripheral and central neural circuits responsible for the nausea and vomiting have not been extensively studied. In the next section we will outline what is known of the functional neuroanatomy of this system in relation to the reflex circuitry of the brain-gut circuit mediating emesis.

## 3. The endocannabinoid system at sites in the brain and gastrointestinal tract involved in nausea and vomiting

The key components of the brain-gut circuitry mediating emesis have been well described (Andrews and Horn, 2006; Hornby, 2001). As outlined above, emesis can be initiated peripherally or centrally. However, most commonly, emesis is evoked from the gastrointestinal tract by ingestion of toxins, including bacteria or bacterial products, or food that is not tolerated. It may also be caused by drugs such as the cancer chemotherapeutic agent cisplatin and radiation. In most of these examples, the initial trigger for emesis is the release of serotonin (5-HT) from enterochromaffin cells that are distributed throughout the epithelium of the gastrointestinal tract (Andrews and Bhandari, 1993; Naylor and Rudd, 1996; Rojas and Slusher, 2012). Serotonin activates 5-$HT_3$ and/or 5-$HT_4$ receptors on vagal primary afferent nerves, whose cell bodies are located in the nodose ganglia. Vagal afferents innervating the proximal gastrointestinal tract may also be activated by distension and/or the release of enteric neurotransmitters in the vicinity of vagal afferent endings in the mucosa, myenteric plexus or muscle layers of the wall of the gut. When effectively stimulated, vagal afferents activate circuits in the dorsal vagal complex of the brainstem (Boissonade et al.,

1994; Hornby, 2001; Miller and Ruggiero, 1994). The dorsal vagal complex consists of the nucleus of the solitary tract, area postrema and dorsal motor nucleus of the vagus. Circulating emetogens can also directly activate neurons in the area postrema, which is a circumventricular organ that lies outside of the blood-brain barrier (Miller and Leslie, 1994). Cerebral and vestibular inputs are also integrated at the level of the nucleus of the solitary tract. The integrative circuitry of the nucleus of the solitary tract initiates appropriate motor responses that involve activation of the respiratory, gastric, salivatory, esophageal, laryngeal and hypoglossal neural centres in the brainstem and spinal cord (Carpenter, 1990; Miller, 1999). These motor centres elicit the characteristic and stereotyped behaviours of emesis.

The brain centres that elicit nausea are far less clearly defined than those involved in emesis. They are clearly distinct from those involved in emesis and are certainly localized in the forebrain. Early studies from Penfield and Faulk (1955) revealed that stimulation of the insular cortex elicited nausea in some patients undergoing surgery for intractable epilepsy. As well, stimulation of the insular cortex has been shown to produce vomiting in humans (Fiol et al., 1988; Catenoix et al., 2008) and other animals (Kaada, 1951). In rats, inactivation of the visceral insular cortex (granular) reduced lithium chloride (LiCl)-induced malaise (Contreras et al., 2007). Contreras et al. (2007) suggested that this region of the insular cortex (which is also involved in craving for drugs; Naqvi and Bechara, 2009; Forget et al., 2010) may be responsible for sensing strong deviations from a “well-being state” (e.g., Craig, 2002). However, recent functional magnetic resonance imaging studies have revealed an extensive network of brain regions activated by visually-evoked nausea (Napadow, 2013). Phasic and sustained increases in BOLD signals were identified with increasing degrees of nausea. Increasing nausea was associated with increasing phasic activation in the ventral putamen, amygdala and the locus coeruleus; brain regions known to process emotion, stress and fear conditioning. With higher levels of nausea intensity, sustained activation was noted in the insular, anterior cingulate, premotor, and orbitofrontoal cortices and the primary and secondary somatosensory cortices. In addition, subcortical activation was noted in the putamen, ventral tegmental area and nucleus accumbens; a broad network of interoceptive, limbic, somatosensory, and cognitive processing brain areas (Napadow, 2013). Some of these regions are also important in integrating vestibular inputs, and so are likely the common centres for the development of nausea, but further experimental studies are required to substantiate whether nausea evoked from different stimuli activate the same brain regions. Of particular relevance to this paper are findings discussed in more detail below that the anti-nausea effects of a $CB_1$ receptor agonist are mediated by an action in the insular cortex (Limebeer et al, 2013), suggesting it may have a prominent role as a central substrate for nausea.

$CB_1$ receptors are widely distributed in the brain and periphery and are in essence found in all the brain regions and peripheral neural structures described above. Direct evidence for the presence of $CB_1$ receptors on 5-HT containing enterochromaffin cells is lacking, but in both rats (that do not vomit) and the house musk shrew (that does vomit) $CB_1$ receptor agonists reduce intestinal 5-HT release, suggesting that enterochromaffin cells express functional $CB_1$ receptors (Hu et al., 2007; Rutkowska and Gliniak, 2009). Of particular interest are the observations that the $CB_1$ agonist WIN 55,212-2 reduced 5-HT release evoked by the emetogenic Staphylococcal enterotoxin (Hu et al., 2007). These results suggest that 5-HT release from enterochromaffin cells might be selectively targeted to reduce emesis triggered by peripheral stimuli, cancer chemotherapeutics or radiation treatment. It remains to be determined if this strategy would be effective. $CB_1$ receptors are found on the vagal afferent neurons in the nodose ganglion (Burdyga et al., 2004; Partosoedarso et al., 2003). Of interest is the fact that these receptors are regulated by the feeding state of the animal. Fed animals have low levels of $CB_1$ expression whereas the levels of $CB_1$ receptor increase with fasting (Burdyga et al., 2004). The expression of these

receptors are not only regulated by circulating hormones such as leptin, but also cannabinoid receptor agonists including anandamide (Burdyga et al., 2004, 2010; Jelsing et al., 2009). Whether $CB_1$ receptors on vagal afferent neurons are involved in the control of nausea and vomiting is not well understood.

$CB_1$ receptors are found in the forebrain, midbrain and brainstem regions described above, in differing densities and in varying locations in the cell. For example, in the locus coeruleus, $CB_1$ receptors were not only found presynaptically, as expected, but also on postsynaptic somatodendritic compartments (Scavone et al., 2010). The highest density of $CB_1$ receptors are in the cortex, amygdala and basal ganglia, with lower densities in the nucleus accumbens, ventral tegmental area and brainstem regions (Mackie, 2005). In the cortex the density of distribution of $CB_1$ receptors varies according the different layers. Throughout the brain there are varying degrees of colocalization with the two main classical transmitters; $CB_1$ seems universally to colocalize with GABA, where it regulates inhibitory transmitter release, but in only some locations does it colocalize with glutamate to regulate excitation (Freund et al., 2003; Kano et al., 2009; Mackie, 2005). Moreover, in neurons the efficiency of the coupling of $CB_1$ receptor to the G protein signaling molecules differs: in GABA neurons it is weakly coupled, whereas in glutamate neurons this coupling is far stronger (Steindel et al., 2013). This implies that lower doses of cannabinoids may elicit effects on glutamatergic synapses whilst GABA synapses may require higher doses of cannabinoids to be effective. Currently, the specific synaptic pathways regulating nausea have not been defined well enough to know which neuronal populations control this sensory experience. Likewise for vomiting, whilst the synaptic circuitry of the dorsal vagal complex is well understood, the specific synaptic events underlying this behavior have not yet been defined. $CB_1$ receptors are nevertheless found in the DVC (Derbenev et al., 2004; Moldrich and Wenger, 2000; Partosoedarso et al., 2003; Sharkey et al., 2007; Suárez et al., 2010; Van Sickle et al., 2001; 2003). $CB_1$ receptors are also found on dopaminergic, noradrenergic and other transmitter containing neurons in the brain regions involved in the control of nausea and vomiting (Freund et al., 2003; Kano et al., 2009; Mackie, 2005).

In general, a detailed description of the other components of the endocannabinoid system in the brain regions regulating nausea and vomiting is lacking. Van Sickle *et al.* (2005) made the discovery that $CB_2$ receptors were present in the dorsal vagal complex of the ferret and were involved in the regulation of emesis. These functional and neuroanatomical studies have not been extended with regard to nausea. Nevertheless, $CB_2$ receptors are more widely distributed in the brain, including in some of the regions identified above that are involved in nausea, such as the amygdala, striatum, nucleus accumbens and cortex (Brusco et al., 2008; Gong et al., 2006). Interestingly, they have also been described in the vestibular nuclei (Baek et al., 2008), but the functional implications of this for motion sickness remain to be determined. It is not yet clear if they are present in the insular cortex of emetic species. Unlike $CB_1$ receptors, $CB_2$ receptors appear to be postsynaptically localized and may regulate neuronal excitability by unique mechanisms, as well as through more traditional cannabinoid signaling. For example, $CB_2$ receptors were recently described in the prefrontal cortex to be intracellular, regulating neuronal excitability though calcium-activated chloride channels (den Boon et al., 2012). Another interesting feature of the $CB_2$ receptor in the brain is that it may form functional heteromers with the $CB_1$ receptor (Callén et al., 2012). One specific characteristic of these heteromeric receptors is that they are bidirectionally cross-antagonized with both $CB_1$ and $CB_2$ receptor antagonists. This opens up interesting possibilities for therapeutics, but needs to be examined more thoroughly since clearly both receptors need to be in the same anatomical location for this to be happening – and in many brain regions they appear distinct.

Far less is known of the other components of the endocannabinoid system, namely the biosynthetic and degradative enzyme systems involved in the production and breakdown of the endocannabinoids. FAAH was described in neurons of the dorsal motor nucleus of the vagus and it appears also to be expressed in the ferret area postrema (Van Sickle et al., 2001), but not that of the rat (Suárez et al., 2010). MAGL is expressed in the area postrema in the rat (Suárez et al., 2010), but has not been anatomically localized in species that vomit, but it is present in brain of house musk shrews by whole brain analysis (Sticht et al., 2012). DAGLα is not found in the area postrema, and NAPE-PLD and DAGLβ are only weakly expressed, suggesting endocannabinoids are not major transmitters in this region of the brain (Suárez et al., 2010). In other brainstem nuclei involved in emesis, DAGL and NAPE-PLD have not been examined. In the brain regions involved in nausea there have not been extensive examinations of the distribution of the enzymes of endocannabinoid biosynthesis, though FAAH and MAGL are present in some of these regions, such as the nucleus accumbens and the amygdala (Dinh et al., 2002; Gulyas et al., 2004; Tsou et al., 1998).

Much more work is required to examine in detail the endocannabinoid system in the brain regions involved in nausea and vomiting, despite the functional evidence for the effectiveness of this system in regulating these functions, as we shall describe below.

## 4. Anti-emetic effects of cannabinoids and endocannabinoids

Cannabis is a well-known anti-emetic whose actions have been extensively reviewed (Cotter, 2009; Darmani and Chebolu, 2013; Izzo and Sharkey, 2010; Parker et al., 2011; Tramèr et al., 2001). Following the isolation of $\Delta^9$-THC, the mechanism and site of action of cannabinoids were established. In humans and animal models, plant-derived cannabinoids, synthetic cannabinoids and endocannabinoids inhibit emesis evoked peripherally or centrally with drugs or natural stimuli. Cannabinoids block both acute and delayed emesis. Where it has been examined, these effects are mediated by $CB_1$ receptors in the DVC (Darmani, 2001a, 2001b; Darmani et al., 2003b; Ray et al., 2009; Van Sickle et al., 2003). Interestingly, there is dissociation between the antiemetic doses of $\Delta^9$-THC and effects of $\Delta^9$-THC on impairing motor function (Darmani, 2001b; Darmani and Crim, 2005).

The role of $CB_2$ receptors in the anti-emetic actions of cannabinoids is less well established. Van Sickle *et al*. (2005) demonstrated that in the ferret the anti-emetic actions of the endocannabinoid 2-AG were blocked by a $CB_2$ receptor antagonist, which did not block the anti-emetic effects of anandamide or $\Delta^9$-THC. Neither were the effects of the synthetic cannabinoid WIN55,212-2 blocked by a $CB_2$ receptor antagonist in the ferret or $\Delta^9$-THC and synthetic cannabinoids CP55,940 and WIN55,212-2 in the least shrew (Darmani, 2001c; Darmani et al., 2003b; Simoneau et al., 2001). Because they lack psychotropic effects, $CB_2$ receptor agonists represent potential anti-emetic therapeutics, but this has yet to be tested clinically.

We will focus the rest of this section on compounds that alter the levels of endogenous cannabinoids and the role of the endocannabinoid system in the regulation of emesis. Administration of $CB_1$ receptor antagonists to humans is frequently associated with nausea and vomiting (Després et al., 2009; Kipnes et al., 2010; Pi-Sunyer et al., 2006). In animals that vomit, $CB_1$ receptor antagonists either initiate vomiting or potentiate emesis evoked by an emetogen (Darmani, 2001a; Sharkey et al., 2007; Van Sickle et al., 2001). Taken at face value, these results initially suggested that there is a tonic release of endocannabinoids giving rise to anti-emetic tone, presumably in the brainstem sites that regulate emesis. However, in these studies the receptor antagonists used are in fact “inverse agonist / receptor antagonists” (Bergman et al., 2008; Pertwee et al., 2010) and these findings were subsequently challenged when it was shown that the centrally acting “neutral” $CB_1$ receptor

antagonist AM4113 did not potentiate emesis (and similar compounds do not cause nausea, as we discuss below) (Chambers et al., 2007). Exactly what property of the inverse agonists is responsible for their pro-emetic action has not been discovered, although they do release serotonin and dopamine in the brainstem of the least shrew (Darmani et al., 2003a), which may contribute to these actions. Assuming it is the inverse agonist activity that causes this effect, these data are consistent with the notion that there is constitutive receptor activity in the brainstem. But it still remains to be determined where in the synaptic circuitry $CB_1$ receptors are acting and whether or not this is the case, because, as we shall illustrate below, further evidence supports the notion of an anti-emetic endocannabinoid tone.

Compounds that increase the availability of endogenous cannabinoids have the potential to harness the anti-emetic power of the endocannabinoid system in a locally restricted manner, given the “on demand” nature of endocannabinoid release (Alger and Kim, 2011). That is, when the emetic circuitry is activated the local release of endocannabinoids acting at cannabinoid receptors would limit the extent of this activation. This concept has been tested and whilst it holds true in some circumstances, there are some conflicting data.

Early studies using the compound VDM11 that was initially reported as an endocannabinoid transport inhibitor revealed efficacious anti-emetic actions in both ferrets and the least shrew against morphine 6-glucuronde and apomorphine, respectively (Darmani et al., 2005; Van Sickle et al., 2005). In the ferret, this effect was interestingly inhibited by both $CB_1$ and $CB_2$ receptor antagonists (Van Sickle et al., 2005). Similarly, AM404, an analogous compound to VDM11, blocks acute but not delayed emesis induced by cisplatin, but not that caused by copper sulphate or apomorphine (Chu et al., 2010); the receptor mechanism of action of AM404 was not examined. These compounds and others like them were recently shown to inhibit the association of anandamide with fatty acid binding proteins, rather than a membrane transporter (Kaczocha et al., 2012). So exactly where it is having an effect and how this action occurs remains an enigma. One possible explanation is that they are acting as FAAH inhibitors and raising the local levels of endocannabinoids. The FAAH inhibitor, URB597, is a particularly promising compound in treatment of nausea and vomiting, because it has no known psychoactive effects (Fegley et al, 2003; Gobbi et al, 2005). URB597 was shown to be anti-emetic against morphine 6 glucuronide in the ferret (Van Sickle et al., 2005), but not against apomorphine in this species (Percie du Sert et al., 2010); but in the least shrew, it is pro-emetic and does not prevent vomiting evoked by cisplatin or apomorphine (Darmani et al., 2005), which argues against this possibility in this species.

More recently, URB597 was tested in the house musk shrew against cisplatin- and nicotine-induced emesis (Parker et al., 2009). URB597 given alone or together with anandamide blocked cisplatin-induced emesis, whilst anandamide (5mg/kg) was ineffective when given alone. Nicotine-induced emesis was also attenuated by URB597 and this effect was reversed by the $CB_1$ receptor antagonist rimonabant, in a dose that alone was not pro-emetic (Parker et al., 2009). Further support for the role of endocannabinoids in the regulation of emesis was obtained by blocking MAGL. Raising 2-AG levels with the selective inhibitor JZL184 was also an effective strategy to block LiCl-induced vomiting in the house musk shrew (Sticht et al., 2011). As before, this was shown to be sensitive to $CB_1$ receptor antagonists, but in neither case were the effects of $CB_2$ receptor antagonists examined with either JZL184 or URB597 (Parker et al., 2009; Sticht et al., 2011). These data tell us that FAAH and MAGL inhibitors, and drugs like VDM11 offer the potential for new anti-emetic strategies. Why the least shrew behaves differently in response to these treatments remains slightly unclear. It may be that endocannabinoids are metabolized differently in this species or that for some reason the emetic circuitry is subtly different in these animals. However, it should also be said, that in most of the studies noted above in the ferret and the house musk shrew, full dose-response curves for the various cannabinoid agonists and antagonists, as

well as enzyme inhibitors have not be performed. Different conclusions might be drawn depending on the nature of the results obtained conducting such studies.

Before moving on to discuss the anti-nausea effects of cannabinoids and endocannabinoids, it is important to consider possible synergistic actions with other receptor systems, notably 5-$HT_3$ and TRPV1. As noted above, anandamide is an intracellular TRPV1 agonist and acts at these receptors to inhibit emesis in the ferret (Sharkey et al., 2007). Similarly, $\Delta^9$-THC at low doses was more efficacious against cisplatin-induced emesis in the house musk shrew when combined with a low dose of a 5-$HT_3$ antagonist, than when given alone (Kwiatkowska et al., 2004), but full dose-response studies were not conducted. In the least shrew, limited potentiation at low doses of $\Delta^9$-THC was also observed (Wang et al., 2009). These studies suggest there is a potential that some of the actions of the endocannabinoid system involve other receptor systems – not limited only to these two. However, the extent to which such interactions actually occur are not clear and future studies should consider them in order to explain more fully the potential of utilizing the endocannabinoid system in novel anti-emetic strategies.

## 5. Cannabinoids and endocannabinoids in the control of nausea in humans

There is clearly a need of treatments for acute, delayed and anticipatory nausea in chemotherapy treatment (e.g., Poli-Bigelli et al., 2003). One of the first recognized medicinal benefits of cannabis was for the treatment of nausea (Iversen, 2008). The most investigated compound has been $\Delta^9$-THC (see Cotter, 2009; Tramèr et al., 2001 for reviews); however, other nonpsychoactive compounds in the cannabis plant have recently been reported to also have benefits in preclinical models of nausea and vomiting.

Nabilone (Cesamet) an orally active, synthetic analogue of $\Delta^9$-THC, was licensed for management of chemotherapy-induced nausea and vomiting in 1985, but today is only prescribed after conventional anti-emetics fail. To our knowledge, studies have only compared nabilone with dopamine receptor 2 ($D_2$) receptor antagonists for their anti-emetic/anti-nausea effects in chemotherapy patients. When compared with $D_2$ receptor antagonists in double blind cross-over designs, such as metoclopramide, nabilone treatment resulted in fewer vomiting episodes (Ahmedzai et al., 1983; Herman et al., 1979; Pomeroy et al., 1986; Steele et al., 1980) and reports of nausea on a 3 point scale of severity (Ahmedzai et al., 1983; Dalzell et al., 1986; Herman et al., 1979) in patients taking moderately toxic chemotherapy treatments; however, when given to cancer patients receiving cisplatin chemotherapy, nabilone was only as effective as the $D_2$ receptor antagonist in reducing vomiting (Crawford and Buckman, 1986). Therefore, nabilone is superior to $D_2$ receptor antagonists for the treatment of moderate emesis but probably not for the treatment of severe emesis.

Another orally active, synthetic $\Delta^9$-THC known as dronabinol (Marinol), has also been used as an anti-emetic and was later used as an appetite stimulant (Pertwee, 2009). When compared with Prochlorperazine (a $D_2$ receptor antagonist) or a combination of dronabinol and the $D_2$ receptor antagonist, those patients given the combination treatment had less severe nausea and the duration was significantly shorter than with either agent alone, when they were being treated with moderately emetogenic chemotherapy (Lane et al., 1991). Most recently, Namisol, a tablet containing pure $\Delta^9$-THC, was designed to improve absorption after ingestion. Evidence in healthy adults indicates its rapid onset may be beneficial for rapid therapeutic effects, but no clinical trials have yet been completed to demonstrate its clinical efficacy (Klumpers et al., 2012).

In cancer patients, administration of oral $\Delta^9$-THC has been shown to significantly suppress the experience of nausea and vomiting, in comparison to placebo controls (Chang et al.,

1979; Frytak et al., 1979; Orr et al., 1980; Sallan et al., 1975; Sweet et al., 1981) and when compared to the $D_2$ receptor antagonists available at the time, $\Delta^9$-THC was at least as effective (Carey et al., 1983; Crawford and Buckman, 1986; Cunningham et al., 1988; Frytak et al., 1979; Tramèr et al., 2001; Ungerleider et al., 1984) if not *more* effective (Ekert et al., 1979; Orr and McKernan, 1981) at reducing nausea and vomiting. Clinical evidence suggests that $\Delta^8$-THC suppresses anticipatory nausea in child patients (Abrahamov et al., 1995).

Only one published clinical trial has directly compared the anti-emetic and anti-nausea effects of a cannabinoid with a 5-$HT_3$ receptor antagonist. Meiri et al. (2007) compared dronabinol, ondansetron, or their combination, for efficacy in reducing delayed chemotherapy-induced nausea and vomiting. Dronabinol and ondansetron alone were equally effective in reducing nausea and vomiting, but the combined therapies were no more effective than either agent alone. When assessing severity of nausea alone, dronabinol was more effective than ondansetron for mildly to moderately severe nausea produced by chemotherapy treatments, but not for severe emetogenic treatments. However, there has been no report of a direct comparison of $\Delta^9$-THC and the current first line treatment of 5-$HT_3$ receptor antagonist/dexamethasone/neurokinin 1 receptor antagonist on acute or delayed chemotherapy-induced nausea or vomiting in human chemotherapy patients.

Another chemical compound in cannabis is cannabidiol (CBD), this non-psychoactive cannabinoid is now available as a sublingual spray called Nabidiolex (GW Pharmaceuticals). There are no reports of any specific evaluation of CBD alone to reduce nausea and vomiting in human chemotherapy patients. Interestingly, there have been no reports of the evaluation of combined $\Delta^9$-THC and CBD on emesis or nausea in animal models. However, in humans, a phase II clinical trial evaluated Sativex (an oromucosally administered cannabis-based medicine containing $\Delta^9$-THC and CBD in a 1:1 ratio), taken in conjunction with standard anti-emetic therapies (5-$HT_3$ receptor antagonists), for its ability to control delayed chemotherapy-induced nausea and vomiting (Duran et al., 2010). When compared with placebo, Sativex reduced the incidence of delayed nausea and vomiting and was well tolerated by patients. Fifty-seven percent of Sativex patients experienced no delayed nausea compared to 22% in the placebo group. In terms of emesis, 71% of Sativex patients versus 22% of placebo patients experienced no delayed emesis. These results indicate that $\Delta^9$-THC and CBD in combination may be useful in managing delayed nausea and vomiting in human patients.

The role of endocannabinoids in nausea and vomiting has typically been investigated in animal models with human data rather scarce. However, Choukèr et al. (2010) recently reported lower blood endocannabinoid levels among participants experiencing motion sickness while undergoing parabolic flight maneuvers, whereas anandamide and 2-AG levels were higher among participants who did not experience motion sickness. Moreover, $CB_1$ receptor expression was reduced among participants experiencing motion sickness compared to those unaffected by parabolic flight maneuvers. Interestingly, anandamide increases were observed early during the flight, whereas the 2-AG increases were observed following the flight, suggesting that endocannabinoids may play different roles in reducing both motion sickness and stress induced by parabolic flights (Choukèr et al., 2010).

## 6. Cannabinoid and endocannabinoid regulation of nausea in animal models

Animal models of vomiting have been valuable in elucidating the neural mechanisms of the emetic reflex (Hornby, 2001); however, the central mechanisms regulating nausea are still not well understood (Andrews and Horn, 2006). Considerably greater progress has been

made toward the control of vomiting than the control of nausea. One reason is that nausea is much more difficult to quantify than is vomiting, and therefore, preclinical model development has been challenging. Although vomiting is a gastrointestinal event under control of brainstem structures (Hornby, 2001), it is generally agreed that activation of central forebrain structures is required to produce the distinct sensation of nausea (see above). The gastrointestinal visceral inputs to the brain are well characterized (Cechetto and Saper, 1987), but the way in which they are processed in the forebrain, leading to the sensation of nausea, is only beginning to be understood. One limitation in the preclinical assessment of nausea has been the lack of a reliable animal model of nausea. Of course, we can never know if an animal experiences nausea in the same manner as humans, however, here we describe the current models used to determine the nauseating potential of compounds and to determine the potential of anti-nausea agents that reverse nausea. Such models are essential if we hope to develop new treatments for this distressing disorder in humans. These models do not require the use of an animal capable of vomiting and have been primarily employed in rodents, which lack an emetic reflex. Although rodents lack an emetic reflex, their gastric afferents respond in the same manner to physical and chemical (intragastric copper sulphate and cisplatin) stimulation that precedes vomiting in ferrets, presumably resulting in nausea that precedes vomiting (Billig et al., 2001; Hillsley and Grundy, 1998). Indeed, 5-$HT_3$ receptor antagonists that block vomiting in ferrets also disrupt this preceding neural afferent reaction in rats (Horn et al., 2004), suggesting that the rat detects nausea, but that the vomiting reaction is absent in this species. Indeed, laboratory rats failed to display any of the common coordinated actions indicative of retching or vomiting after emetic stimulation as compared with the musk shrew, using an in-situ brainstem preparation (Horn et al., 2013).

### 6.1 Pica

Consumption of non-nutritive kaolin clay, an example of pica (the eating of a non-food substance), is a putative direct indicator of nausea in rodents. Pica consumption may ameliorate the effects of toxins in the diet (e.g. Mitchell et al., 1976; Rudd et al., 2002). Pica has been reported in several strains of rats and mice exposed to emetic compounds (e.g. Stern et al., 2011); however, in emetic species, such as the house musk shrew, pica has not been demonstrated (Liu et al., 2005; Stern et al., 2011; Yamamoto et al., 2004). Although $\Delta^9$-THC has not been specifically evaluated for its anti-nausea effects in the pica model of increased intake of kaolin, the synthetic $CB_1$ receptor agonist, WIN55,212-2 did not modify pica produced by chronic administration of cisplatin (Vera et al., 2007). To our knowledge, there have been no investigations of the potential of endocannabinoid manipulations to modify pica in rats or mice. Pica has the advantage of being a measure of unconditioned nausea, but it has poor temporal resolution (Stern et al., 2011). In addition, it may be difficult to apply to a species when intake is small, and it can be produced by factors other than nausea, such as stress or pain (Burchfield et al., 1977); therefore, it may not be selectively produced by nausea.

### 6.2 Lying on Belly

Lying on belly in rats (e.g. Bernstein et al., 1992; Parker et al., 1984) or flopping in ferrets (Stern et al., 2011) is another behavior that has been characterised as a nausea-induced response. In rats, this behavior has only been evaluated as a measure of LiCl-induced nausea (e.g. Bernstein et al., 1992; Contreras et al., 2007; Tuerke et al., 2012b). No other emetic agents have been evaluated using this measure. Both area postrema lesions (Bernstein et al. 1992) and interoceptive insular cortex lesions (Contreras et al. 2007) reduce LiCl-induced lying on belly. As well, pretreatment with the 5-$HT_3$ receptor antagonist, ondansetron, reduces LiCl-induced lying on belly in rats (Tuerke et al., 2012b). There have been no reports of the effect of cannabinoid manipulations on the behavior of lying on belly in rats.

A major limitation in this measure of nausea-induced behavior, however, is the difficulty in discriminating lying on belly from non-specific locomotor suppression (e.g. Tuerke et al., 2012b); therefore, this measure may not be a specific model of nausea-induced behavior.

### 6.3 Conditioned Flavor Avoidance and Conditioned Gaping

Other commonly employed rodent measures of nausea are conditioned flavor avoidance learning (e.g. Garcia et al., 1974) and conditioned gaping reactions in the taste reactivity test (Grill and Norgren, 1978). These are not direct measures of nausea, but rely upon conditioning. Conditioned flavor avoidance is a measure of an animal's reluctance to consume flavors of foods that have been previously paired with nausea-inducing treatments. Indeed, high doses (8–10 mg/kg) of the $CB_1$ inverse agonists AM251 (McLaughlan et al., 2005) and rimonabant (DeVry et al., 2004) have been shown to produce conditioned avoidance of flavored solution as well as conditioned gaping reactions (McLaughlan et al., 2005), but lower doses (3 and 5 mg/kg) that are also effective in reducing food intake failed to produce conditioned avoidance of flavored food pellets in a two choice test, even after 4 conditioning trials (Chambers et al., 2006). On the other hand, $CB_1$ receptor neutral antagonists, AM6545 (Cluny et al., 2010), AM6527 (Limebeer et al., 2010) and AM4113 (Sink et al., 2008) all failed to produce both conditioned flavor avoidance and conditioned gaping at a high dose (10 mg/kg). These results suggest that it is the inverse agonist effect of rimonabant that is responsible for the side effect of nausea in human clinical trials (Després et al., 2009; Kipnes et al., 2010; Pi-Sunyer et al., 2006). Somewhat paradoxically, the $CB_1$agonists CP55,940 (0.1 mg/kg; McGregor et al., 1996) and $\Delta^9$-THC (1.5 mg/kg −2.5 mg/kg; Parker and Gilles, 1995; Schramm-Sapyta et al., 2007) also produce conditioned flavor avoidance and conditioned place avoidance. Yet, low doses of $\Delta^9$-THC (0.3 and 1 mg/kg) and nabilone (0.01 and 0.03 mg/kg), but not levonantrodol (0.03 an 0.06 mg/kg) have also been reported to attenuate flavor avoidance induced by cyclophosphamide in CD-1 mice (Landauer et al., 1985). Since conditioned flavor avoidance can be produced even by rewarding drugs in non-emetic rodents it is not a particularly selective measure of nausea (see Parker review in current issue).

In contrast to conditioned flavor avoidance, conditioned gapingreactions appear to be more selective measure of conditioned nausea which is only produced by emetic drugs and consistently prevented by anti-emetic drugs (see Grill and Norgren, 1978; Pelchat et al., 1983; Parker review in present volume). Much of the work on the effects of cannabinoids and endocannabinoids on nausea in rodents using this model is reviewed by Parker et al. (2011). Here we update this review.

Clearly, low doses of $CB_1$ agonists (0.5 mg/kg $\Delta^9$-THC, Limebeer and Parker, 1999; 0.001–0.01 HU-210, Parker et al., 2003) attenuate nausea in the conditioned gaping model, an effect that is reversed by rimonabant (see Parker et al., 2011). At low doses (1–5 mg/kg, i.p.) the nonpsychoactive phytocannabinoid, CBD, also reduces these nausea-induced behaviors (without affecting any measures of motor activity) by its action as an indirect agonist of 5-$HT_{1A}$ receptors in the dorsal raphe nucleus (Rock et al., 2012; Parker et al., 2011). By acting as an agonist of the somatodendritic 5-$HT_{1A}$ autoreceptors located in the dorsal raphe, CBD would be expected to reduce the release of 5-HT in forebrain regions (e.g. possibly the interoceptive insular cortex, Tuerke et al., 2012a) to ultimately suppress toxin-induced nausea. The currently employed anti-anxiety compound buspirone acts as a partial 5-HT1A agonist. In humans, buspirone resulted in a reduction of self-report nausea scores in healthy human patients participating in nutrient drink test to assess gastric functioning (Chial et al., 2003). In this test, participants consume the maximum tolerated volume of a nutrient drink at the rate of 30 ml/min and 30 min later symptoms of bloating, fullness, nausea and pain are assessed. Buspirione (10 mg twice orally) selectively lowered nausea ratings in this test. On

the other hand, intravenously administered busprione was ineffective in preventing postoperative nausea and vomiting (Kranke et al., 2012).

The non-psychoactive carboxylic acidic precursor of CBD, cannabidiolic acid (CBDA), is present in the fresh cannabis plant and slowly loses its acidic function (decarboxylates) in the plant in response to heating (e.g. when cannabis is smoked). Recent evidence indicates that CBDA (0.1 and/or 0.5 mg/kg, i.p.) potently interferes with motion-, LiCl-, and cisplatin-induced vomiting in the house musk shrew (Bolognini et al., 2012). CBDA also reduced acute nausea produced by LiCl, an effect that was prevented by pretreatment with the 5-$HT_{1A}$ receptor antagonist, WAY100635, and not by rimonabant. CBDA also increased the ability of the 5-$HT_{1A}$ receptor agonist, 8-OH-DPAT, to potently stimulate [$^{35}$S]GTPγS binding to rat brainstem membrane, again without activating $CB_1$ receptors *in vitro* or *in vivo*. More recently, CBDA has been shown to reduce acute nausea at a dose as low as 0.5 μg/kg (Rock and Parker, 2013a). As well, a subthreshold dose of CBDA (0.1 μg/kg, i.p.) enhanced the ability of a mildly effective dose of ondansetron (1 μg/kg) (Rock and Parker, 2013a) and an ineffective dose (0.3 mg/g) of metoclopramide (Rock and Parker, 2013b) to reduce LiCl-induced acute nausea in the rat flavor induced gaping model. Interestingly, both CBD (Mechoulam et al., 2002) and CBDA (Rock and Parker, 2013a) have no effect on locomotor activity or any of the commonly measured $CB_1$ mediated psychoactive behaviors.

The carboxylic acidic precursor of $\Delta^9$-THC is tetrahydrocannabinolic acid (THCA, Gaoni and Mechoulam, 1964). In the fresh plant, THCA is decarboxylated to $\Delta^9$-THC by heating or burning. Interestingly, no psychotomimetic activity was observed when THCA was administered to: rhesus monkeys at doses up to 5 mg/kg (intravenously, i.v.), mice at doses up to 20 mg/kg (i.p.), and dogs at doses up to 7 mg/kg (Grunfeld and Edery, 1969). Recent results (Rock et al., 2013) indicate that THCA (0.5 and 0.05 mg/kg, i.p.) reduced LiCl-induced vomiting in the house musk shrew, an effect that was reversed with rimonabant pretreatment. THCA (0.05 mg /kg, i.p.) also reduced conditioned gaping elicited by a flavour, without modifying saccharin palatability or conditioned taste avoidance. The suppression of LiCl-induced gaping was not simply the result of conversion of the THCA to THC once administered, because when administered at a dose of 0.05 mg/kg, i.p., $\Delta^9$-THC did not suppress this nausea induced behaviour.

Endocannabinoids are also effective in reducing conditioned gaping in rats. As reviewed by Parker et al. (2011) inhibition of FAAH-mediated hydrolysis of anandamide by URB597 has been shown to suppress LiCl-induced conditioned gaping in rats, with an even greater suppressive effect when co-administered with exogenous anandamide (Cross-Mellor et al., 2007). As well, most recently, inhibition of anandamide reuptake by ARN272 also suppresses this nausea-induced behavior (O'Brien et al., 2013). Both of these effects were reversed by the rimonabant, indicating a $CB_1$ mediated effect. More recently, the endocannabinoid, 2-AG, like anandamide, has been shown to reduce nausea in rats. Pretreatment with exogenous 2-AG dose-dependently suppresses the establishment of LiCl induced conditioned gaping (Sticht et al., 2011). However, unlike the anti-nausea effects of anandamide, those of 2-AG do not seem to be entirely dependent on $CB_1$ receptors since they can be reversed by the cyclooxygenase inhibitor, indomethacin (Sticht et al., 2011), but not by the $CB_1$ or $CB_2$ receptor antagonists, AM251 and AM630, respectively. Interestingly, the suppression of conditioned gaping following concomitant pretreatment with the MAGL inhibitor, JZL184, and exogenous 2-AG was partially reversed by a $CB_1$ receptor antagonist (Sticht et al., 2011), suggesting that decreased 2-AG turnover reduces nausea, in part, through an action at $CB_1$ receptors. However, since cyclooxygenase inhibition blocks the anti-nausea effects of 2-AG, it appears that 2-AG acts through several mechanisms to modulate LiCl-induced nausea. Further research is necessary to clarify the precise role of downstream endocannabinoid metabolites in the suppression of nausea.

As described above, rimonabant and AM251 produce both vomiting and nausea at high doses by acting as $CB_1$ inverse agonists. At lower doses than those that produce the nausea-induced behavior of gaping (2.5 mg/kg), both AM251 (Limebeer et al., 2010) and rimonabant (Parker et al., 2003) potentiated the gaping produced by LiCl. On the other hand, the $CB_1$ receptor neutral antagonists (without inverse agonist effects), AM4113 (Sink et al., 2007), AM6527 (Limebeer et al., 2010) and AM6545 (Cluny et al., 2010; Limebeer et al., 2010) do not produce conditioned flavor avoidance, nausea-induced conditioned gaping or potentiated LiCl-induced conditioned gaping reactions. Therefore, the nausea inducing effects of rimonabant and AM251 appear to be mediated by their inverse agonism effects at the $CB_1$ receptor.

As indicated above, it is generally understood that nausea is regulated by central forebrain regions. Recent evidence indicates that at least one the forebrain region regulating nausea is the visceral insular cortex. Ablation of this region (Kiefer and Orr, 1992) and selective serotonin lesions of this region (Tuerke et al., 2012a) prevents LiCl-induced conditioned gaping reactions. As well, intracranial administration of ondansetron to this region attenuates nausea induced gaping reactions (Tuerke et al., 2012). Of particular interest, the location of the $CB_1$ receptors mediating the anti-nausea actions appear to be in the visceral insular cortex (Limebeer et al., 2012). Delivery of the $CB_1$ agonist, HU-210, to the visceral insular cortex, but not to the gustatory insular cortex, interfered with the establishment of LiCl-induced gaping reactions in rats. Such interference was prevented by co-administration of the $CB_1$ inverse agonist/antagonist AM251 at a dose that had no effect on its own. Interestingly, however, the nausea-inducing effects of the $CB_1$ inverse agonist/antagonist AM251 was not evoked by administration into this brain region (Limebeer et al., 2012).

## 7. Contextually-elicited conditioned gaping reactions: A model of anticipatory nausea

Rats not only display conditioned gaping reactions when re-exposed to a flavor previously paired with a nausea-inducing drug, but they also display conditioned gaping reactions when re-exposed to a context previously paired with a nausea-inducing drug (Chan et al., 2009; Limebeer et al., 2008; Rock et al., 2008;). As well, the house musk shrew also displays conditioned retching when re-exposed to a context previously paired with toxin-induced vomiting (Parker and Kemp, 2001; Parker et al., 2006). These contextually elicited conditioned gaping or retching reactions represent animal models of anticipatory nausea analogous to that experienced by human chemotherapy patients, which can be produced following 3–4 conditioning trials. In human chemotherapy patients, when anticipatory nausea develops, the classic anti-emetic agent ondansetron is ineffective in reducing this symptom (Hickok et al., 2003); likewise rats and shrews pretreated with ondansetron do not show a suppression of contextually-elicited gaping and retching reactions, respectively (Limebeer et al., 2006; Parker and Kemp, 2001; Parker et al., 2006; Rock et al., 2008). On the other hand, $\Delta^9$- THC, URB597 and CBD all reduce these contextually-elicited conditioned nausea reactions (Parker et al., 2011). More recently, it has been shown that CBDA (Bolognini et al., 2012) were more potent than CBD and $\Delta^9$-THC respectively in attenuation of contextually-elicited conditioned gaping in rats. CBDA potently suppresses nausea and vomiting in a $5\text{-}HT_{1A}$ receptor dependent manner (Bolognini et al., 2012). Since these compounds are both non-psychoactive, they are promising candidates for the treatment of anticipatory nausea, as there is no current therapeutic available once anticipatory nausea does develop. Currently, patients are given non-specific anti-anxiety drugs.

Similarly, endocannabinoid enzyme inhibitors reduce contextually-elicited conditioned gaping in rats. The FAAH inhibitor, URB597, interfered with both the establishment and expression of conditioned gaping to an illness-paired context in a dose dependent manner

(Rock et al., 2008). Since rimonabant reversed these effects, they were most likely mediated by elevated anandamide. Recently, Limebeer et al. (2013) evaluated the potential of the dual FAAH /MAGL inhibitor, JZL195, on its own and combined with anandamide and 2-AG, to reduce anticipatory nausea in the rat model. JZL195 suppressed conditioned gaping and by elevation of anandamide, but not 2-AG, an effect that was reversed by rimonabant (Limebeer et al., 2013). The suppressant effect of JZL195 was potentiated by co-administration of anandamide or 2-AG. On its own anandamide, but not 2-AG, also suppressed contextually elicited gaping, again reversed by rimonabant.

## 8. Cannabis and hyperemesis: the paradoxical effect of chronic exposure to cannabis

Heavy chronic cannabis use in some people, frequently young ones, leads to a constellation of symptoms that include abdominal pain, recurrent nausea and intractable cyclic vomiting (Galli et al, 2011; Nicolson et al., 2012; Simonetto et al., 2012). This syndrome was first reported about 10 years ago (Allen et al., 2004). These symptoms are, of course, exactly the opposite of what has been outlined above and hence represent a paradoxical effect of cannabis. Relief from these symptoms can be obtained from hot baths and showers, but standard anti-emetic treatments are not particularly effective (Galli et al, 2011; Nicholson et al., 2012; Simonetto et al., 2012). The mechanisms underlying these effects are entirely unknown, but are speculated to be either the buildup of a toxic chemical from the cannabis plant, or are due to a downregulation of cannabinoid receptors due to the high exposure to ligand. There are no animal models for this syndrome, which perhaps warrants further investigations. Given the relatively recent appearance of this condition, it would seem likely that recent developments in the horticulture of the plant may be responsible.

## 9. Future directions in using the endocannabinoid system in the treatment of nausea and vomiting

As can be appreciated from the discussion in the previous sections, we believe that the endocannabinoid system has the potential to be used for the treatment of nausea and likely as an adjunct therapy for the treatment of emesis, particularly delayed emesis, where current therapies are limited in their degree of efficacy. There are, however, many gaps in our knowledge, most of which were highlighted above. One of the biggest limitations is the very widespread nature of the $CB_1$ receptor and the many critical functions in the synaptic control of neurotransmission that it subserves. Any compounds that either act directly at the receptor or increase (or reduce) ligand availability, have the potential to radically alter brain functions beyond that of nausea and vomiting. So, for example, enhancing endocannabinoid biosynthesis, which would, on the face of it, seem like a good anti-emetic strategy, is unlikely to be specific and might lead to many unwanted side-effects. Reducing endocannabinoid metabolism seems to carry with it a lot of potential and to date, side-effects of FAAH and MAGL inhibitors seem to be rather minimal, at least in animal models. Currently, another major limitation of advancing endocannabinoid therapies for the treatment of nausea and vomiting is actually our knowledge of the specific roles played by the two endocannabinoids anandamide and 2-AG. By inference from use of FAAH and MAGL inhibitors, both seem to be important, but more sophisticated approaches are required to identify the specific functional contributions of each. As noted above, understanding the role of $CB_2$ receptors, particularly in nausea, also remains an important direction in research. There may be an opportunity to utilize these receptors for treatments, though as for $CB_1$ receptors, their widespread nature may limit or restrict the use of such therapies.

Nausea and vomiting are frequently debilitating conditions that require substantial effort and cost to manage. Advances in recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system have revealed significant potential for therapeutic approaches to be developed. Future efforts aimed at developing new endocannabinoid-based anti-nausea and anti-emetic therapies are clearly warranted.

## Acknowledgments

Original work in the authors' laboratories is supported by the Canadian Institutes of Health Research (KAS), the Natural Sciences and Engineering Research Council of Canada (LAP) and NIH grants-NIDA 12605 and CA115331 (ND). KAS is the recipient of a Killam Annual Professorship and holds the Crohn's & Colitis Foundation of Canada Chair in Inflammatory Bowel Disease Research at the University of Calgary. LAP is the recipient of a Tier 1 Canada Research Chair in behavioural neuroscience at University of Guelph.

## References

Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci. 1995; 56:2097–2102. [PubMed: 7776837]

Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. Br J Can. 1983; 48:657–63.

Alger BE, Kim J. Supply and demand for endocannabinoids. Trends Neurosci. 2011; 34:304– 315. [PubMed: 21507493]

Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004; 53:1566–1570. [PubMed: 15479672]

Andrews PL, Bhandari P. The 5-hydroxytryptamine receptor antagonists as antiemetics: preclinical evaluation and mechanism of action. Eur J Cancer. 1993; 29A(Suppl 1):S11–S16. [PubMed: 8427719]

Andrews PL, Horn CC. Signals for nausea and emesis: Implications for models of upper gastrointestinal diseases. Auton Neurosci. 2006; 125:100–115. [PubMed: 16556512]

Baek JH, Zheng Y, Darlington CL, Smith PF. Cannabinoid CB2 receptor expression in the rat brainstem cochlear and vestibular nuclei. Acta Otolaryngol. 2008; 128:961–967. [PubMed: 19086305]

Bergman J, Delatte MS, Paronis CA, Vemuri K, Thakur GA, Makriyannis A. Some effects of CB1 antagonists with inverse agonist and neutral biochemical properties. Physiol Behav. 2008; 93:666–670. [PubMed: 18076956]

Bernstein IL, Chavez M, Allen D, Taylor EM. Area postrema mediation of physiological and behavioral effects of lithium chloride in the rat. Brain Res. 1992; 575:132–7. [PubMed: 1324085]

Billig I, Yates BJ, Rinaman L. Plasma hormone levels and central c-Fos expression in ferrets after systemic administration of cholecystokinin. Am J Physiol Regul Integr Comp Physiol. 2001; 281:R1243–55. [PubMed: 11557633]

Blankman JL, Cravatt BF. Chemical probes of endocannabinoid metabolism. Pharmacol Rev. 2013; 65:849–871. [PubMed: 23512546]

Blankman JL, Simon GM, Cravatt BF. A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. Chem Biol. 2007; 14:1347–1356. [PubMed: 18096503]

Boissonade FM, Sharkey KA, Davison JS. Fos expression in ferret dorsal vagal complex after peripheral emetic stimuli. Am J Physiol. 1994; 266:R1118–R1126. [PubMed: 8184953]

Bolognini D, Rock EM, Cluny NL, Cascio MG, Limebeer CL, Duncan M, Stott CG, Javid FA, Parker LA, Pertwee RG. Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. Br J Pharmacol. 2013; 168:1456–1470. [PubMed: 23121618]

Borison HL, Borison R, McCarthy LE. Phylogenic and neurologic aspects of the vomiting process. J Clin Pharmacol. 1981; 21:23S–29S. [PubMed: 6117573]

Borison HL, Wang SC. Physiology and pharmacology of vomiting. Pharmacol Rev. 1953; 5:193–230. [PubMed: 13064033]

Brusco A, Tagliaferro PA, Saez T, Onaivi ES. Ultrastructural localization of neuronal brain CB2 cannabinoid receptors. Ann NY Acad Sci. 2008; 1139:450–457. [PubMed: 18991892]

Burchfield SR, Elich MS, Woods SC. Geophagia in response to stress and arthritis. Physiol Behav. 1977; 19:265–7. [PubMed: 564521]

Burdyga G, Lal S, Varro A, Dimaline R, Thompson DG, Dockray GJ. Expression of cannabinoid CB1 receptors by vagal afferent neurons is inhibited by cholecystokinin. J Neurosci. 2004; 24:2708–2715. [PubMed: 15028763]

Burdyga G, Varro A, Dimaline R, Thompson DG, Dockray GJ. Expression of cannabinoid CB1 receptors by vagal afferent neurons: kinetics and role in influencing neurochemical phenotype. Am J Physiol Gastrointest Liver Physiol. 2010; 299:G63–G69. [PubMed: 20430875]

Callen L, Moreno E, Barroso-Chinea P, Moreno-Delgado D, Cortes A, Mallol J, Casado V, Lanciego JL, Franco R, Lluis C, Canela EI, McCormick PJ. Cannabinoid receptors CB1 and CB2 form functional heteromers in brain. J Biol Chem. 2012; 287:20851–20865. [PubMed: 22532560]

Carey MP, Burish TG, Brenner DE. Delta-9-tetrahydrocannabinol in cancer chemotherapy: research problems and issues. Ann Intern Med. 1983; 99:106–14. [PubMed: 6305249]

Carpenter DO. Neural mechanisms of emesis. Can J Physiol Pharmacol. 1990; 68:230–236. [PubMed: 2178747]

Castillo PE, Younts TJ, Chavez AE, Hashimotodani Y. Endocannabinoid signaling and synaptic function. Neuron. 2012; 76:70–81. [PubMed: 23040807]

Catenoix H, Isnard J, Guénot M, Petit J, Remy C, Mauguiére F. The role of the anterior insular cortex in ictal vomiting: A stereotactic electroencephalography study. Epilepsy Behav. 2008; 13:560–563. [PubMed: 18627792]

Cechetto DF, Saper CB. Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J Comp Neurol. 1987; 262:27–45. [PubMed: 2442207]

Chambers AP, Koopmans HS, Pittman QJ, Sharkey KA. AM 251 produces sustained reductions in food intake and body weight that are resistant to tolerance and conditioned taste aversion. Br J Pharmacol. 2006; 147:109–116. [PubMed: 16258524]

Chambers AP, Vemuri VK, Peng Y, Wood JT, Olszewska T, Pittman QJ, Makriyannis A, Sharkey KA. A neutral CB1 receptor antagonist reduces weight gain in rat. Am J Physiol Regul Integr Comp Physiol. 2007; 293:R2185–R2193. [PubMed: 17959701]

Chan MY, Cross-Mellor SK, Kavaliers M, Ossenkopp K-P. Lipopolysaccharide (LPS) blocks the acquisition of LiCl-induced gaping in a rodent model of anticipatory nausea. Neurosci Lett. 2009; 450:301–305. [PubMed: 19059465]

Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, Simon RM, Rosenberg SA. Delata-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Ann Intern Med. 1979; 91:819–24. [PubMed: 293141]

Chial HJ, Camilleri M, Burton D, Thomforde G, Olden KW, Stephens D. Selective effects of serotonergic psychoactive agents on gastrointestinal functions in health. Am J Physiol Gastrointest Liver Physiol. 2003; 28:G130–137. [PubMed: 12488239]

Choukèr A, Kaufmann I, Kreth S, Hauer D, Feuerecker M, Thieme D, Vogeser M, Thiel M, Schelling G. Motion sickness, stress and the endocannabinoid system. PLoS One. 2010; 5:e10752. [PubMed: 20505775]

Chu KM, Ngan MP, Wai MK, Yeung CK, Andrews PL, Percie du SN, Rudd JA. Olvanil: a non-pungent TRPV1 activator has anti-emetic properties in the ferret. Neuropharmacol. 2010; 58:383–391.

Cluny NL, Vemuri K, Chambers A, Limebeer CL, Bedard H, Wood J, Lutz B, Zimmer A, Parker LA, Makriyannis A, Sharkey KA. A novel, peripherally restricted, cannabinoid 1 (CB1) receptor antagonist AM6545 reduces food intake and body weight, but does not cause malaise, in rodents. Br J Pharmacol. 2010; 161:629–42. [PubMed: 20880401]

Contreras M, Ceric F, Torrealba F. Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium. Science. 2007; 318:655–658. [PubMed: 17962567]

Cotter J. Efficacy of crude marijuana and synthetic delta-9-Tetrahydrocannabinol as treatment for chemotherapy-induced nausea and vomiting: a systematic literature review. Oncol Nurs Forum. 2009; 36:345–52. [PubMed: 19596652]

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 2002; 3:655–666. [PubMed: 12154366]

Crawford SM, Buckman R. Nabilone and metoclopramide in the treatment of nausea and vomiting due to cisplatinum: a double blind study. Med Oncol Tumor Pharmacother. 1986; 3:39–42. [PubMed: 3010011]

Cross-Mellor SK, Ossenkopp KP, Piomelli D, Parker LA. Effects of the FAAH inhibitor, URB597, and anandamice on lithium-induced taste reactivity responses: a measure of nausea in rats. Psychopharmacol. 2007; 190:135–143.

Cunningham D, Bradley CJ, Forrest GJ, Hutcheon AW, Adams L, Sneddon M, Harding M, Kerr DJ, Soukop M, Kaye SB. A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. Eur J Cancer Clin Oncol. 1988; 24:685–9. [PubMed: 2838294]

Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. Arch Dis Childhood. 1986; 61:502–5. [PubMed: 3013104]

Darmani NA. Delta(9)-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB(1) receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacol. 2001a; 24:198–203.

Darmani NA. Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB(1) receptors in the least shrew. Pharmacol Biochem Behav. 2001b; 69:239–249. [PubMed: 11420092]

Darmani NA. The cannabinoid CB1 receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55, 212-2. Eur J Pharmacol. 2001c; 430:49–58. [PubMed: 11698062]

Darmani, NA.; Chebolu, S. The role of endocannabinoids and arachidonic acid metabolites in emesis. In: Murillo-Rodriguez, E., editor. Endocannabinoids: Molecular, Pharmacological, Behavioral and Clinical Features. Bentham Science Publishers; Sharjah, UAE: 2013. p. 25-59.

Darmani NA, Crim JL. Delta-9-tetrahydrocannabinol differentially suppresses emesis versus enhanced locomotor activity produced by chemically diverse dopamine $D_2/D_3$ receptor agonists in the least shrew (*Cryptotis parva*). Pharmacol Biochem Behav. 2005; 80:35–44. [PubMed: 15652378]

Darmani NA, Janoyan JJ, Kumar N, Crim JL. Behaviorally active doses of the CB1 receptor antagonist SR 141716A increase brain serotonin and dopamine levels and turnover. Pharmacol Biochem Behav. 2003; 75:777–787. [PubMed: 12957219]

Darmani NA, McClanahan BA, Trinh C, Petrosino S, Valenti M, Di Marzo V. Cisplatin increases brain 2-arachidonoylglycerol (2-AG) and concomitantly reduces intestinal 2-AG and anandamide levels in the least shrew. Neuropharmacol. 2005; 49:502–513.

Darmani NA, Sim-Selley LJ, Martin BR, Janoyan JJ, Crim JL, Parekh B, Breivogel CS. Antiemetic and motor-depressive actions of CP55,940: cannabinoid CB1 receptor characterization, distribution, and G-protein activation. Eur J Pharmacol. 2003; 459:83–95. [PubMed: 12505537]

De Vry J, Schreiber R, Eckel G, Jentzsch KR. Behavioral mechanisms underlying inhibition of food-maintained responding by the cannabinoid receptor antagonist/inverse agonist SR141716A. Eur J Pharmacol. 2004; 483:55–63. [PubMed: 14709326]

den Boon FS, Chameau P, Schaafsma-Zhao Q, van Aken W, Bari M, Oddi S, Kruse CG, Maccarrone M, Wadman WJ, Werkman TR. Excitability of prefrontal cortical pyramidal neurons is modulated by activation of intracellular type-2 cannabinoid receptors. Proc Natl Acad Sci US A. 2012; 109:3534–3539.

Derbenev AV, Stuart TC, Smith BN. Cannabinoids suppress synaptic input to neurones of the rat dorsal motor nucleus of the vagus nerve. J Physiol. 2004; 559:923–938. [PubMed: 15272041]

Despres JP, Ross R, Boka G, Almeras N, Lemieux I. Effect of rimonabant on the high-triglyceride/low-HDL-cholesterol dyslipidemia, intraabdominal adiposity, and liver fat: the ADAGIO-Lipids trial. Arterioscler Thromb Vasc Biol. 2009; 29:416–423. [PubMed: 19112166]

Di Marzo V, De Petrocellis L. Why do cannabinoid receptors have more than one endogenous ligand? Philos. Trans R Soc Lond B Biol Sci. 2012; 367:3216–3228.

Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, Kathuria S, Piomelli D. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci US A. 2002; 99:10819–10824.

Duran M, Pérez E, Abanades S, Vidal X, Saura C, Majem M, Arriola E, Rabanal M, Pastor A, Farré M, Rams N, Laporte JR, Capellà D. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol. 2010; 70:656–63. [PubMed: 21039759]

Edvinsson L, Villalon CM, MaassenVanDenBrink A. Basic mechanisms of migraine and its acute treatment. Pharmacol Ther. 2012; 136:319–333. [PubMed: 22939884]

Egertova M, Simon GM, Cravatt BF, Elphick MR. Localization of N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) expression in mouse brain: A new perspective on N-acylethanolamines as neural signaling molecules. J Comp Neurol. 2008; 506:604–615. [PubMed: 18067139]

Ekert H, Waters KD, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Australia. 1979; 2:657–9. [PubMed: 231736]

Fegley D, Gaetani S, Duranti A, Tontini A, Mor M, Tarzia G, et al. Characterization of the fatty acid amide hydrolase inhibitor cyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl ester (URB-597): Effects on anandamide and oleoylethanolamide deactivation. J Pharmacol Exp Ther. 2005; 313:352–358. [PubMed: 15579492]

Fiol M, Leppik IE, Mireless R, Maxwell R. Ictus emeticus and the insular cortex. Epilepsy Res. 1988; 2:127–131. [PubMed: 3197686]

Forget B, Pushparaj A, Le FB. Granular insular cortex inactivation as a novel therapeutic strategy for nicotine addiction. Biol Psychiatry. 2010; 68:265–271. [PubMed: 20299008]

Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev. 2003; 83:1017–1066. [PubMed: 12843414]

Frytak S, Moertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connell MJ, Schutt AJ, Schwartau NW. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. Ann Intern Med. 1979; 91:825–30. [PubMed: 517882]

Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev. 2011; 4:241–249. [PubMed: 22150623]

Gao Y, Vasilyev DV, Goncalves MB, Howell FV, Hobbs C, Reisenberg M, Shen R, Zhang MY, Strassle BW, Lu P, Mark L, Piesla MJ, Deng K, Kouranova EV, Ring RH, Whiteside GT, Bates B, Walsh FS, Williams G, Pangalos MN, Samad TA, Doherty P. Loss of retrograde endocannabinoid signaling and reduced adult neurogenesis in diacylglycerol lipase knock-out mice. J Neurosci. 2010; 30:2017–2024. [PubMed: 20147530]

Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Amer Chem Soc. 1964; 86:1646–7.

Garcia J, Hankins WG, Rusiniak KW. Behavioral regulation of the milieu interne in man and rat. Science. 1974; 185:824–31. [PubMed: 11785521]

Gobbi G, Vambico FR, Manqieri R, Bortalato M, Campolongo P, Sollinas M, et al. Antidepressant like activity and modulation of brain monominergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci USA. 2005; 102:18620–18625. [PubMed: 16352709]

Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, Uhl GR. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res. 2006; 1071:10–23. [PubMed: 16472786]

Grill HC, Norgren R. The taste reactivity test. I: Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res. 1978; 14:263–79. [PubMed: 630409]

Grunfeld Y, Edery H. Psychopharmacological activity of the active constituents of hashish and some related cannabinoids. Psychopharmacol. 1969; 14:200–10.

Gulyas AI, Cravatt BF, Bracey MH, Dinh TP, Piomelli D, Boscia F, Freund TF. Segregation of two endocannabinoid-hydrolyzing enzymes into pre- and postsynaptic compartments in the rat hippocampus, cerebellum and amygdala. Eur J Neurosci. 2004; 20:441–458. [PubMed: 15233753]

Gyombolai P, Pap D, Turu G, Catt KJ, Bagdy G, Hunyady L. Regulation of endocannabinoid release by G proteins: a paracrine mechanism of G protein-coupled receptor action. Mol Cell Endocrinol. 2012; 353:29–36. [PubMed: 22075205]

Herman TS, Einhorn LH, Jones SE, Nagy C, Chester AB, Dean JC, Furnas B, Williams SD, Leigh SA, Dorr RT, Moon TE. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. New Engl J Med. 1979; 300:1295–7. [PubMed: 375088]

Hesketh, PJ. Management of nausea and vomiting in cancer and cancer treatment. Jones and Bartlett Learning; Boston: 2005.

Hickok JT, Roscoe JA, Morrow GR, King DK, Atkins JN, Fitch TR. Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5-hydroxytryptamine-3 antiemetics: a university of Rochester James P. Wilmot cancer center community clinical oncology program study of 360 cancer patients treated in the community. Cancer. 2003; 97:2880–6. [PubMed: 12767103]

Hillsley K, Grundy D. Serotonin and cholecystokinin activate different populations of rat mesenteric vagal afferents. Neurosci Lett. 1998; 255:63–6. [PubMed: 9835215]

Horn CC. Why is the neurobiology of nausea and vomiting so important? Appetite. 2008; 50:430–434. [PubMed: 17996982]

Horn CC, Richardson EJ, Andrews PL, Friedman ML. Differential effects on gastrointestinal and hepatic vagal afferent fibers in the rat by the anti-cancer agent cisplatin, Auton. Neurosci. 2004; 115:74–81.

Horn CC, Kimball BA, Wang H, Kaus J, Dienel S, Nagy A, Gathright GR, Yates BJ, Andrews PLR. Why can't rodents vomit? A comparative behavioral, anatomical, and physiological study. PLOS One. 2013; 8 in press.

Hornby PJ. Central neurocircuitry associated with emesis. Am J Med. 2001; 111(Suppl 8A):106S–112S. [PubMed: 11749934]

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002; 54:161–202. [PubMed: 12037135]

Hu DL, Zhu G, Mori F, Omoe K, Okada M, Wakabayashi K, Kaneko S, Shinagawa K, Nakane A. Staphylococcal enterotoxin induces emesis through increasing serotonin release in intestine and it is downregulated by cannabinoid receptor 1. Cell Microbiol. 2007; 9:2267–2277. [PubMed: 17517065]

Iversen, LL. The Science of Marijuana. 2. New York: Oxford University Press; 2008.

Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther. 2010; 126:21–38. [PubMed: 20117132]

Jelsing J, Larsen PJ, Vrang N. The effect of leptin receptor deficiency and fasting on cannabinoid receptor 1 mRNA expression in the rat hypothalamus, brainstem and nodose ganglion. Neurosci Lett. 2009; 463:125–129. [PubMed: 19596404]

Kaada BR. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat, and dog; A study of responses from the limbic, subcallosal, orbito-insular, piriform and temporal cortex, hippocampus-fornix and amygdala. Acta Physiol Scand. 1951; (Suppl 24):1–262.

Kaczocha M, Vivieca S, Sun J, Glaser ST, Deutsch DG. Fatty acid-binding proteins transport N-acylethanolamines to nuclear receptors and are targets of endocannabinoid transport inhibitors. J Biol Chem. 2012; 287:3415–3424. [PubMed: 22170058]

Kalant H. Medicinal use of cannabis: history and current status. Pain Res Manag. 2001; 6:80– 91. [PubMed: 11854770]

Kano M, Ohno-Shosaku T, Hashimotodani Y, Uchigashima M, Watanabe M. Endocannabinoid-mediated control of synaptic transmission. Physiol Rev. 2009; 89:309–380. [PubMed: 19126760]

Katona I, Freund TF. Multiple functions of endocannabinoid signaling in the brain. Annu Rev Neurosci. 2012; 35:529–558. [PubMed: 22524785]

Kiefer SW, Orr MR. Taste avoidance, but not aversion, learning in rats lacking gustatory cortex. Behav Neurosci. 1992; 106:140–146. [PubMed: 1313241]

Kim J, Alger BE. Reduction in endocannabinoid tone is a homeostatic mechanism for specific inhibitory synapses. Nat Neurosci. 2010; 13:592–600. [PubMed: 20348918]

Kipnes MS, Hollander P, Fujioka K, Gantz I, Seck T, Erondu N, Shentu Y, Lu K, Suryawanshi S, Chou M, Johnson-Levonas AO, Heymsfield SB, Shapiro D, Kaufman KD, Amatruda JM. A one-year study to assess the safety and efficacy of the CB1R inverse agonist taranabant in overweight and obese patients with type 2 diabetes. Diabetes Obes Metab. 2010; 12:517–531. [PubMed: 20518807]

Klumpers LE, Beumer TL, van Hasselt JG, et al. Novel Δ(9)-tetrahydrocannabinol formulation Namisol® has beneficial pharmacokinetics and promising pharmacodynamic effects. Br J Clin Pharmacol. 2012; 74:42–53. [PubMed: 22680341]

Koch KL. Diabetic gastropathy: gastric neuromuscular dysfunction in diabetes mellitus: a review of symptoms, pathophysiology, and treatment. Dig Dis Sci. 1999; 44:1061–1075. [PubMed: 10389675]

Kranke P, Röhm KD, Diemunsch P, Gan TJ, Apfel CC, Eberhart L, Minkowitz HS, Wallenborn J, Chassard D, Lebuffe G, Fox GM, Tramér MR. Intravenous buspirone for the prevention of postoperative nausea and vomiting. Eur J Clin Pharmacol. 2012; 68:1465–72. [PubMed: 22546895]

Kwiatkowska M, Parker LA, Burton P, Mechoulam R. A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the Suncus murinus (house musk shrew). Psychopharmacol (Berl). 2004; 174:254–259.

Landauer MR, Balster RL, Harris LS. Attenuation of cyclophosphamide-induced taste aversions in mice by prochlorperazeine, delta 9-tetraydrocannabinol, nbilone and levonantradol. 1985; 23:259–66.

Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JL, Hamm J, Salva K, Wiernik PH, Holroyde CP, Hammill S, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Symptom Manag. 1991; 6:352–9.

Leung D, Saghatelian A, Simon GM, Cravatt BF. Inactivation of N-acyl phosphatidylethanolamine phospholipase D reveals multiple mechanisms for the biosynthesis of endocannabinoids. Biochemistry. 2006; 45:4720–4726. [PubMed: 16605240]

Limebeer CL, Abdullah RA, Rock EM, Imhof E, Wang K, Lichtman AH, Parker LA. Effect of manipulation of the endocannabinoid system on contextually-elicited conditioned gaping reactions in rats: A model of anticipatory nausea. Psychopharmacol. 2013 In press.

Limebeer CL, Hall G, Parker LA. Exposure to a lithium-paired context elicits gaping in rats: A model of anticipatory nausea. Physiol Behav. 2006; 88:398–403. [PubMed: 16737724]

Limebeer CL, Krohn JP, Cross-Mellor S, Ossenkopp K-P, Parker LA. Exposure to a context previously associated with toxin (LiCl)- or motion-induced sickness elicits conditioned gaping in rats: Evidence in support of a model of anticipatory nausea. Behav Brain Res. 2008; 187:33–40. [PubMed: 17897732]

Limebeer CL, Parker LA. Delta-9-tetrahydrocannabinol interferes with the establishment and the expression of conditioned rejection reactions produced by cyclophosphamide: a rat model of nausea. Neurorep. 1999; 10:3769–3772.

Limebeer CL, Rock EM, Mechoulam R, Parker LA. The anti-nausea effects of CB1 agonists are mediated by an action at the visceral insular cortex. Br J Pharmacol. 2012; 167:126–36.

Limebeer CL, Vemuri VK, Bedard H, Lang ST, Ossenkopp KP, Makriyannis A, Parker LA. Inverse agonism of cannabinoid CB1 receptors potentiates LiCl-induced nausea in the conditioned gaping model in rats. Br J Pharmacol. 2010; 161:336–349. [PubMed: 20735419]

Liu J, Wang L, Harvey-White J, Huang BX, Kim HY, Luquet S, Palmiter RD, Krystal G, Rai R, Mahadevan A, Razdan RK, Kunos G. Multiple pathways involved in the biosynthesis of anandamide. Neuropharmacology. 2008; 54:1–7. [PubMed: 17631919]

Liu J, Wang L, Harvey-White J, Osei-Hyiaman D, Razdan R, Gong Q, Chan AC, Zhou Z, Huang BX, Kim HY, Kunos G. A biosynthetic pathway for anandamide. Proc Natl Acad Sci US A. 2006; 103:13345–13350.

Liu YL, Malik N, Sanger GJ, Friedan MI, Andrews PL. Pica--a model of nausea? Species differences in response to cisplatin. Physiol Behav. 2005; 85:271–7. [PubMed: 15939445]

Long JZ, Cravatt BF. The metabolic serine hydrolases and their functions in mammalian physiology and disease. Chem Rev. 2011; 111:6022–6063. [PubMed: 21696217]

Long JZ, Nomura DK, Vann RE, Walentiny DM, Booker L, Jin X, Burston JJ, Sim-Selley LJ, Lichtman AH, Wiley JL, Cravatt BF. Dual blockade of FAAH and MAGL identifies behavioral processes regulated by endocannabinoid crosstalk in vivo. Proc Natl Acad Sci US A. 2009; 106:20270–20275.

Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol. 2005:299–325. [PubMed: 16596779]

Marrs WR, Blankman JL, Horne EA, Thomazeau A, Lin YH, Coy J, Bodor AL, Muccioli GG, Hu SS, Woodruff G, Fung S, Lafourcade M, Alexander JP, Long JZ, Li W, Xu C, Moller T, Mackie K, Manzoni OJ, Cravatt BF, Stella N. The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors. Nat Neurosci. 2010; 13:951–957. [PubMed: 20657592]

McGregor IS, Issakidis CN, Prior G. Aversive effects of the synthetic cannabinoid CP 55,940 in rats. Pharmacol Biochem Behav. 1996; 53:657–664. [PubMed: 8866969]

McLaughlin PJ, Winston KM, Limebeer CL, Parker LA, Makriyannis A, Salamone JD. The cannabinoid CB1 antagonist AM 251 produces food avoidance and behaviors associated with nausea but does not impair feeding efficiency in rats. Psychopharmacol. 2005; 180:286–93.

Mechoulam R, Parker LA, Gallily R. Cannabidiol: An overview of some chemical and pharmacological aspects. Part II: Pharmacological aspects. J Clin Pharmacol. 2002; 12:5–20.

Mechoulam R, Parker LA. The endocannabinoid system and the brain. Ann Rev Psychol. 2013; 64:21–47. [PubMed: 22804774]

Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang HM, Baranowski V. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Cur Med Res Opin. 2007; 23:533–43.

Miller AD. Central mechanisms of vomiting. Dig Dis Sci. 1999; 44:39S–43S. [PubMed: 10490038]

Miller AD, Leslie RA. The area postrema and vomiting. Front Neuroendocrinol. 1994; 15:301–320. [PubMed: 7895890]

Miller AD, Ruggiero DA. Emetic reflex arc revealed by expression of the immediate- early gene c-fos in the cat. J Neurosci. 1994; 14:871–888. [PubMed: 8301366]

Min R, Di Marzo V, Mansvelder HD. DAG lipase involvement in depolarization-induced suppression of inhibition: does endocannabinoid biosynthesis always meet the demand? Neuroscientist. 2010; 16:608–613. [PubMed: 20837870]

Mitchell D, Wells C, Hoch N, Lind K, Woods SC, Mitchell LK. Poison induced pica in rats. Physiol Behav. 1976; 17:691–7. [PubMed: 1034944]

Moldrich G, Wenger T. Localization of the CB1 cannabinoid receptor in the rat brain. An immunohistochemical study. Peptides. 2000; 21:1735–1742. [PubMed: 11090929]

Mott TF, McConnon ML, Rieger BP. Subacute to chronic mild traumatic brain injury. Am Fam Physician. 2012; 86:1045–1051. [PubMed: 23198672]

Napadow V, Sheehan JD, Kim J, Lacount LT, Park K, Kaptchuk TJ, Rosen BR, Kuo B. The brain circuitry underlying the temporal evolution of nausea in humans. Cereb Cortex. 2013; 23:806–813. [PubMed: 22473843]

Naqvi NH, Bechara A. The hidden island of addiction: the insula. Trends Neurosci. 2009; 32:56–67. [PubMed: 18986715]

Naylor RJ, Rudd JA. Mechanisms of chemotherapy/radiotherapy-induced emesis in animal models. Oncology. 1996; 53(Suppl 1):8–17. [PubMed: 8692557]

Nicolson SE, Denysenko L, Mulcare JL, Vito JP, Chabon B. Cannabinoid hyperemesis syndrome: a case series and review of previous reports. Psychosomatics. 2012; 53:212–219. [PubMed: 22480624]

O'Brien LD, Limebeer CL, Rock EM, Bottegoni G, Piomelli D, Parker LA. Prolonged anandamide availability by anandamide transport inhibition attenuates nausea-induced behaviour in rats, and vomiting in shrews (*Suncus murinus)*. Br J Pharmacol. 2013 In press.

Onaivi ES, Ishiguro H, Gu S, Liu QR. CNS effects of CB2 cannabinoid receptors: beyond neuro-immuno-cannabinoid activity. J Psychopharmacol. 2012; 26:92–103. [PubMed: 21447538]

Orr LE, McKernan JF. Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. J Clin Pharmacol. 1981; 21:76S–80. [PubMed: 6271846]

Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Arch Intern Med. 1980; 140:1431–1433. [PubMed: 6254456]

Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? Prog. Lipid Res. 2011; 50:193–211.

Parker LA, Gillies T. THC-induced place and taste aversions in Lewis and Sprague- Dawley rats. Behav Neurosci. 1995; 109:71–8. [PubMed: 7734082]

Parker LA, Hills K, Jensen K. Behavioral CRs elicited by a lithium- or an amphetamine-paired contextual test chamber. Ann Learn Behav. 1984; 12:307–15.

Parker LA, Kemp SW. Tetrahydrocannabinol (THC) interferes with conditioned retching in Suncus murinus: An animal model of anticipatory nausea and vomiting (ANV). Neurorep. 2001; 12:749–51.

Parker LA, Kwiatkowska M, Mechoulam R. Delta-9-tetrahydrocannabinol and cannabidiol, but not ondansetron, interfere with conditioned retching reactions elicited by a lithium-paired context in *Suncus murinus*: An animal model of anticipatory nausea and vomiting. Physiol Behav. 2006; 87:61–71.

Parker LA, Limebeer CL, Rock EM, Litt DL, Kwiatkowska M, Piomelli D. The FAAH inhibitor URB-597 interferes with cisplatin- and nicotine-induced vomiting in the Suncus murinus (house musk shrew). Physiol Behav. 2009; 97:121–124. [PubMed: 19239915]

Parker LA, Mechoulam R, Schlievert C, Abbott LA, Fudge ML, Burton P. Cannabinoid agonists attenuate and a cannabinoid antagonist potentiates lithium-induced conditioned rejection reactions in a rat model of nausea. Psychopharmacol. 2003; 166:156–162.

Parker LA, Rana SA, Limebeer CL. Conditioned disgust, but not conditioned taste avoidance: A measure of conditioned nausea in rats. Can J Exp Psychol. 2008; 62:198–209. [PubMed: 18778149]

Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol. 2011; 163:1411–1422. [PubMed: 21175589]

Partosoedarso ER, Abrahams TP, Scullion RT, Moerschbaecher JM, Hornby PJ. Cannabinoid1 receptor in the dorsal vagal complex modulates lower oesophageal sphincter relaxation in ferrets. J Physiol. 2003; 550:149–158. [PubMed: 12879865]

Patil CL, Abrams ET, Steinmetz AR, Young SL. Appetite sensations and nausea and vomiting in pregnancy: an overview of the explanations. Ecol Food Nutr. 2012; 51:394–417. [PubMed: 22881357]

Pelchat ML, Grill HJ, Rozin P, Jacobs J. Quality of acquired responses to tastes by *Rattus norvegicus* depends on type of associated discomfort. J Comp Psychol. 1983; 97:140–53. [PubMed: 6307586]

Penfield W, Faulk ME Jr. The insula; further observations on its function. Brain. 1955; 78:445– 470. [PubMed: 13293263]

Percie du SN, Ho WS, Rudd JA, Andrews PL. Cannabinoid-induced reduction in antral pacemaker frequency: a telemetric study in the ferret. Neurogastroenterol Motil. 2010; 22:1257–66. e324. [PubMed: 20731777]

Pertwee RG. Emerging strategies for exploiting cannabinoid receptor agonists as medicines. Br J Pharmacol. 2009; 156:397–411. [PubMed: 19226257]

Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di MV, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). Pharmacol Rev. 2010; 62:588–631. [PubMed: 21079038]

Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or

obese patients: RIO-North America: a randomized controlled trial. JAMA. 2006; 295:761–775. [PubMed: 16478899]

Piomelli D. The molecular logic of endocannabinoid signalling. Nat Rev Neurosci. 2003; 4:873– 884. [PubMed: 14595399]

Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple A, Evans JK, Horgan KJ, Lawson F. Aprepitant Protocol 054 Study Group. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer. 2003; 97:3090–8. [PubMed: 12784346]

Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. Cancer Chemother Pharmacol. 1986; 17:285–8. [PubMed: 3017596]

Ray AP, Chebolu S, Darmani NA. Receptor-selective agonists induce emesis and Fos expression in the brain and enteric nervous system of the least shrew (Cryptotis parva). Pharmacol Biochem Behav. 2009; 94:211–218. [PubMed: 19699757]

Rock EM, Bolognini D, Limebeer CL, Cascio MG, Anavi-Goffer S, Fletcher PJ, Mechoulam R, Pertwee RG, Parker LA. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. Br J Pharmacol. 2012; 165:2620–2634. [PubMed: 21827451]

Rock EM, Kopstick RL, Limebeer CL, Parker LA. Tetrahydrocannabinolic acid reduces nausea-induced conditioned gaping in rats and vomiting in *Suncus murinus*. Br J Pharm. 201310.1111/bph.12316

Rock EM, Limebeer CL, Mechoulam R, Piomelli D, Parker LA. The effect of cannabidiol and URB597 on conditioned gaping (a model of nausea) elicited by a lithium-paired context in the rat. Psychopharmacol. 2008; 196:389–95.

Rock EM, Parker LA. Effect of low doses of cannabidiolic acid and ondansetron on LiCl-induced conditioned gaping (a model of nausea-induced behaviour) in rats. Br J Pharmacol. 2013a; 169:685–692. [PubMed: 23488964]

Rock EM, Parker LA. Suppression of lithium chloride-induced conditioned gaping (a model of nausea-induced behaviour) in rats (using the taste reactivity test) with metoclopramide is enhanced by cannabindiolic acid. Pharmacol Biochem Behav. 2013b In press.

Rojas C, Slusher BS. Pharmacological mechanisms of 5-HT(3) and tachykinin NK(1) receptor antagonism to prevent chemotherapy-induced nausea and vomiting. Eur J Pharmacol. 2012; 684:1–7. [PubMed: 22425650]

Rudd JA, Yamamoto K, Yamatodani A, Takeda N. Differential action of ondansetron and dexamethasone to modify cisplatin-induced acute and delayed kaolin consumption (“pica”) in rats. Eur J Pharmacol. 2002; 454:47–52. [PubMed: 12409004]

Rutkowska M, Gliniak H. The influence of ACEA--a selective cannabinoid CB1 receptor agonist on whole blood and platelet-poor plasma serotonin concentrations. Pharmazie. 2009; 64:598–601. [PubMed: 19827303]

Sallan SE, Zinberg NE, Frei E 3rd. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. New Engl J Med. 1975; 293:795–7. [PubMed: 1099449]

Sanger GJ, Andrews PL. Treatment of nausea and vomiting: gaps in our knowledge. Auton Neurosci. 2006; 129:3–16. [PubMed: 16934536]

Sanu O, Lamont RF. Hyperemesis gravidarum: pathogenesis and the use of antiemetic agents. Expert Opin Pharmacother. 2011; 12:737–748. [PubMed: 21361848]

Savinainen JR, Saario SM, Laitinen JT. The serine hydrolases MAGL, ABHD6 and ABHD12 as guardians of 2-arachidonoylglycerol signalling through cannabinoid receptors. Acta Physiol (Oxf). 2012; 204:267–276. [PubMed: 21418147]

Scavone JL, Mackie K, Van Bockstaele EJ. Characterization of cannabinoid-1 receptors in the locus coeruleus: relationship with mu-opioid receptors. Brain Res. 2010; 1312:18–31. [PubMed: 19931229]

Schmäl F. Neuronal mechanisms and the treatment of motion sickness. Pharmacol. 2013; 91:229–241.

Schramm-Sapyta NL, Cha YM, Chaudhry S, Wilson WA, Swartzwelder HS, Kuhn CM. Differential anxiogenic, aversive, and locomotor effects of THC in adolescent and adult rats. Psychopharmacol (Berl). 2007; 191:867–877.

Sharkey KA, Cristino L, Oland LD, Van Sickle MD, Starowicz K, Pittman QJ, Guglielmotti V, Davison JS, Di Marzo V. Arvanil, anandamide and N-arachidonoyl-dopamine (NADA) inhibit emesis through cannabinoid CB1 and vanilloid TRPV1 receptors in the ferret. Eur J Neurosci. 2007; 25:2773–2782. [PubMed: 17459108]

Sherman PW, Flaxman SM. Nausea and vomiting of pregnancy in an evolutionary perspective. Am J Obstet Gynecol. 2002; 186:S190–S197. [PubMed: 12011885]

Simoneau II, Hamza MS, Mata HP, Siegel EM, Vanderah TW, Porreca F, Makriyannis A, Malan TP Jr. The cannabinoid agonist WIN55,212-2 suppresses opioid-induced emesis in ferrets. Anesthesiol. 2001; 94:882–887.

Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc. 2012; 87:114–119. [PubMed: 22305024]

Sink KS, McLaughlin PJ, Wood JA, Brown C, Fan P, Vemuri VK, Peng Y, Olszewska T, Thakur GA, Makriyannis A, Parker LA, Salamone JD. The novel cannabinoid CB1 receptor neutral antagonist AM4113 suppresses food intake and food-reinforced behavior but does not induce signs of nausea in rats. Neuropsychopharmacol. 2008; 33:946–955.

Steele N, Gralla RJ, Braun DW Jr, Young CW. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. Cancer Treat Rep. 1980; 64:219–24. [PubMed: 6250699]

Steindel F, Lerner R, Haring M, Ruehle S, Marsicano G, Lutz B, Monory K. Neuron- type specific cannabinoid-mediated G protein signalling in mouse hippocampus. J Neurochem. 2013; 124:795–807. [PubMed: 23289830]

Stern, RM.; Koch, KL.; Andrews, PL. Nausea: mechanisms and management. Oxford University Press; Oxford: 2011.

Sticht MA, Long JZ, Rock EM, Limebeer CL, Mechoulam R, Cravatt BF, Parker LA. The MAGL inhibitor, JZL184, attenuates LiCl-induced vomiting in the *Suncus murinus* and 2-AG attenuates LiCl-induced nausea-like behaviour in rats. Br J Pharmacol. 2011; 165:2425–2435. [PubMed: 21470205]

Sticht MA, Long JZ, Rock EM, Limebeer CL, Mechoulam R, Cravatt BF, Parker LA. Inhibition of monoacylglycerol lipase attenuates vomiting in Suncus murinus and 2- arachidonoyl glycerol attenuates nausea in rats. Br J Pharmacol. 2012; 165:2425–2435. [PubMed: 21470205]

Suárez J, Romero-Zerbo SY, Rivera P, Bermudez-Silva FJ, Perez J, de Fonseca FR, Fernandez-Llebrez P. Endocannabinoid system in the adult rat circumventricular areas: an immunohistochemical study. J Comp Neurol. 2010; 518:3065–3085. [PubMed: 20533360]

Sweet DL, Miller NJ, Weddington W, Senay E, Sushelsky L. delta 9- Tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A pilot study. J Clin Pharmacol. 1981; 21:70S–75S. [PubMed: 6271845]

Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ. 2001; 323:16–21. [PubMed: 11440936]

Tsou K, Nogueron MI, Muthian S, Sanudo-Pena MC, Hillard CJ, Deutsch DG, Walker JM. Fatty acid amide hydrolase is located preferentially in large neurons in the rat central nervous system as revealed by immunohistochemistry. Neurosci Lett. 1998; 254:137–140. [PubMed: 10214976]

Tuerke KJ, Limebeer CL, Fletcher PJ, Parker LA. Double dissociation between regulation of conditioned disgust and taste avoidance by serotonin availability at the 5-HT3 receptor in the posterior and anterior insular cortex. J Neurosci. 2012a; 32:13709–13717. [PubMed: 23035083]

Tuerke KJ, Winters BD, Parker LA. Ondansetron interferes with unconditioned lying-on belly and acquisition of conditioned gaping induced by LiCl as models of nausea-induced behaviors in rats. Physiol Behav. 2012b; 105:856–860. [PubMed: 22056540]

Ueda N, Tsuboi K, Uyama T. Enzymological studies on the biosynthesis of N- acylethanolamines. Biochim Biophys Acta. 2010; 1801:1274–1285. [PubMed: 20736084]

Ueda N, Tsuboi K, Uyama T, Ohnishi T. Biosynthesis and degradation of the endocannabinoid 2-arachidonoylglycerol. Biofactors. 2011; 37:1–7. [PubMed: 21328621]

Ungerleider JT, Andrysiak TA, Fairbanks LA, Tesler AS, Parker RG. Tetrahydrocannabinol vs. prochlorperazine. The effects of two antiemetics on patients undergoing radiotherapy. Radiology. 1984; 150:598–599. [PubMed: 6318262]

Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005; 310:329–332. [PubMed: 16224028]

Van Sickle MD, Oland LD, Ho W, Hillard CJ, Mackie K, Davison JS, Sharkey KA. Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology. 2001; 121:767–774. [PubMed: 11606489]

Van Sickle MD, Oland LD, Mackie K, Davison JS, Sharkey KA. Delta9-tetrahydrocannabinol selectively acts on CB1 receptors in specific regions of dorsal vagal complex to inhibit emesis in ferrets. Am J Physiol Gastrointest Liver Physiol. 2003; 285:G566–G576. [PubMed: 12791597]

Vera G, Chiarlone A, Cabezos PA, Pascual D, Martin MI, Abalo R. WIN 55,212-2 prevents mechanical allodynia but not alterations in feeding behaviour induced by chronic cisplatin in the rat. Life Sci. 2007; 81:467–79.

Wang Y, Ray AP, McClanahan BA, Darmani NA. The antiemetic interaction of Delta9-tetrahydrocannabinol when combined with tropisetron or dexamethasone in the least shrew. Pharmacol Biochem Behav. 2009; 91:367–373. [PubMed: 18727934]

Wise LE, Long KA, Abdullah RA, Long JZ, Cravatt BF, Lichtman AH. Dual fatty acid amide hydrolase and monoacylglycerol lipase blockade produces THC-like Morris water maze deficits in mice. ACS Chem Neurosci. 2012; 3:369–378. [PubMed: 22860205]

Yamamoto K, Ngan MP, Takeda N, Yamatodani A, Rudd JA. Differential activity of drugs to induce emesis and pica behavior in Suncus murinus (house musk shrew) and rats. Physiol Behav. 2004; 83:151–6. [PubMed: 15501502]

Yates BJ, Miller AD, Lucot JB. Physiological basis and pharmacology of motion sickness: an update. Brain Res Bull. 1998; 47:395–406. [PubMed: 10052567]

Yoshida T, Fukaya M, Uchigashima M, Miura E, Kamiya H, Kano M, Watanabe M. Localization of diacylglycerol lipase-alpha around postsynaptic spine suggests close proximity between production site of an endocannabinoid, 2-arachidonoyl-glycerol, and presynaptic cannabinoid CB1 receptor. J Neurosci. 2006; 26:4740–4751. [PubMed: 16672646]

# REFERENCE #16

# Cannabinoids in the management of difficult to treat pain

Ethan B Russo

GW Pharmaceuticals, Vashon, WA, USA

**Abstract:** This article reviews recent research on cannabinoid analgesia via the endocannabinoid system and non-receptor mechanisms, as well as randomized clinical trials employing cannabinoids in pain treatment. Tetrahydrocannabinol (THC, Marinol®) and nabilone (Cesamet®) are currently approved in the United States and other countries, but not for pain indications. Other synthetic cannabinoids, such as ajulemic acid, are in development. Crude herbal cannabis remains illegal in most jurisdictions but is also under investigation. Sativex®, a cannabis derived oromucosal spray containing equal proportions of THC (partial $CB_1$ receptor agonist ) and cannabidiol (CBD, a non-euphoriant, anti-inflammatory analgesic with $CB_1$ receptor antagonist and endocannabinoid modulating effects) was approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. Numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain. An Investigational New Drug application to conduct advanced clinical trials for cancer pain was approved by the US FDA in January 2006. Cannabinoid analgesics have generally been well tolerated in clinical trials with acceptable adverse event profiles. Their adjunctive addition to the pharmacological armamentarium for treatment of pain shows great promise.

**Keywords:** cannabinoids, tetrahydrocannabinol, cannabidiol, analgesia, pain management, multiple sclerosis

## Introduction

Chronic pain represents an emerging public health issue of massive proportions, particularly in view of aging populations in industrialized nations. Associated facts and figures are daunting: In Europe, chronic musculoskeletal pain of a disabling nature affects over one in four elderly people (Frondini et al 2007), while figures from Australia note that older half of older people suffer persistent pain, and up to 80% in nursing home populations (Gibson 2007). Responses to an ABC News poll in the USA indicated that 19% of adults (38 million) have chronic pain, and 6% (or 12 million) have utilized cannabis in attempts to treat it (ABC News et al 2005).

Particular difficulties face the clinician managing intractable patients afflicted with cancer-associated pain, neuropathic pain, and central pain states (eg, pain associated with multiple sclerosis) that are often inadequately treated with available opiates, antidepressants and anticonvulsant drugs. Physicians are seeking new approaches to treatment of these conditions but many remain concerned about increasing governmental scrutiny of their prescribing practices (Fishman 2006), prescription drug abuse or diversion. The entry of cannabinoid medicines to the pharmacopoeia offers a novel approach to the issue of chronic pain management, offering new hope to many, but also stoking the flames of controversy among politicians and the public alike.

This article will attempt to present information concerning cannabinoid mechanisms of analgesia, review randomized clinical trials (RCTs) of available and emerging

Correspondence: Ethan Russo, MD
20402 81st Avenue SW, Vashon, WA 98070, USA
Tel +1 206 408 7082
Fax +1 866 234 7757
Email erusso@gwpharm.com

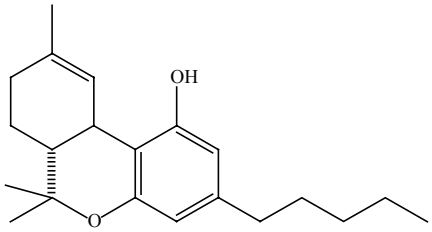
cannabinoid agents, and address the many thorny issues that have arisen with clinical usage of herbal cannabis itself ("medical marijuana"). An effort will be made to place the issues in context and suggest rational approaches that may mitigate concerns and indicate how standardized pharmaceutical cannabinoids may offer a welcome addition to the pharmacotherapeutic armamentarium in chronic pain treatment.

## Cannabinoids and analgesic mechanisms

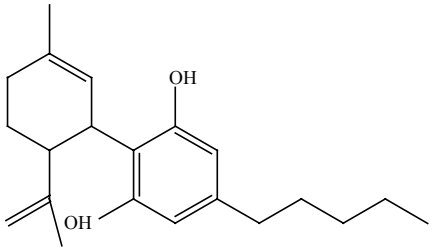
Cannabinoids are divided into three groups. The first are naturally occurring 21-carbon terpenophenolic compounds found to date solely in plants of the *Cannabis* genus, currently termed phytocannabinoids (Pate 1994). The best known analgesic of these is $\Delta^9$-tetrahydrocannabinol (henceforth, THC)(Figure 1), first isolated and synthesized in 1964 (Gaoni and Mechoulam 1964). In plant preparations and whole extracts, its activity is complemented by other "minor" phytocannabinoids such as cannabidiol (CBD) (Figure 1), cannabis terpenoids and flavonoids, as will be discussed subsequently.

Long before mechanisms of cannabinoid analgesia were understood, structure activity relationships were investigated and a number of synthetic cannabinoids have been developed and utilized in clinical trials, notably nabilone (Cesamet®, Valeant Pharmaceuticals), and ajulemic acid (CT3, IP-751, Indevus Pharmaceuticals) (Figure 1).

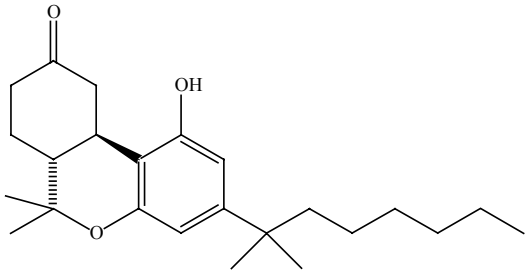
In 1988, the first cannabinoid receptor was identified ($CB_1$) (Howlett et al 1988) and in 1993, a second was described ($CB_2$) (Munro et al 1993). Both are 7-domain G-protein coupled receptors affecting cyclic-AMP, but $CB_1$ is more pervasive throughout the body, with particular predilection to nociceptive areas of the central nervous system and spinal cord (Herkenham et al 1990; Hohmann et al 1999), as well as the peripheral nervous system (Fox et al 2001; Dogrul et al 2003) wherein synergy of activity between peripheral and central cannabinoid receptor function has been demonstrated (Dogrul et al 2003). $CB_2$, while commonly reported as confined to lymphoid and immune tissues, is also proving to be an important mediator for suppressing both pain and inflammatory processes (Mackie 2006). Following the description of cannabinoid receptors, endogenous ligands for these were discovered: anandamide (arachidonylethanolamide, AEA) in 1992 in porcine brain (Devane et al 1992), and 2-arachidonylglycerol (2-AG) in 1995 in canine gut tissue (Mechoulam et al 1995) (Figure 1). These endocannabinoids both act as retrograde messengers on G-protein coupled receptors, are synthesized on demand,



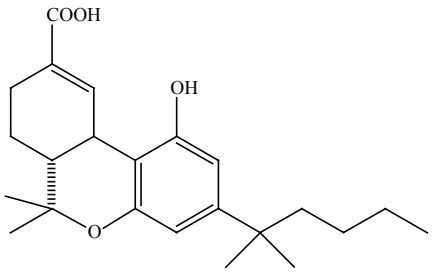

delta-9-tetrahydrocannabinol (THC)




cannabidiol




nabilone (Cesamet)




ajulemic acid

**Figure 1** Molecular structures of four cannabinoids employed in pain treatment.

and are especially active on glutamatergic and GABA-ergic synapses. Together, the cannabinoid receptors, their endogenous ligands ("endocannabinoids") and metabolizing enzymes comprise the endocannabinoid system (ECS) (Di Marzo et al 1998), whose functions have been prosaically termed to be "relax, eat, sleep, forget and protect" (p. 528). The endocannabinoid system parallels and interacts at many points with the other major endogenous pain control systems:

endorphin/enkephalin, vanilloid/transient receptor potential (TRPV), and inflammatory. Interestingly, our first knowledge of each pain system has derived from investigation of natural origin analgesic plants, respectively: cannabis (*Cannabis sativa*, *C. indica*) (THC, CBD and others), opium poppy (*Papaver somniferun*) (morphine, codeine), chile peppers (eg, *Capsicum annuum*, *C. frutescens*, *C. chinense*) (capsaicin) and willow bark (*Salix* spp.) (salicylic acid, leading to acetylsalicylic acid, or aspirin). Interestingly, THC along with AEA and 2-AG, are all partial agonists at the $CB_1$ receptor. Notably, no endocannabinoid has ever been administered to humans, possibly due to issues of patentability and lack of commercial feasibility (Raphael Mechoulam, pers comm 2007). For an excellent comprehensive review of the endocannabinoid system, see Pacher et al (2006), while Walker and Huang have provided a key review of antinociceptive effects of cannabinoids in models of acute and persistent pain (Walker and Huang 2002).

A clinical endocannabinoid deficiency has been postulated to be operative in certain treatment-resistant conditions (Russo 2004), and has received recent support in findings that anandamide levels are reduced over controls in migraineurs (Sarchielli et al 2006), that a subset of fibromyalgia patients reported significant decreased pain after THC treatment (Schley et al 2006), and the active role of the ECS in intestinal pain and motility in irritable bowel syndrome (Massa and Monory 2006) wherein anecdotal efficacy of cannabinoid treatments have also been claimed.

The endocannabinoid system is tonically active in control of pain, as demonstrated by the ability of SR141716A (rimonabant), a $CB_1$ antagonist, to produce hyperalgesia upon administration to mice (Richardson et al 1997). As mentioned above, the ECS is active throughout the neuraxis, including integrative functions in the periacqueductal gray (Walker et al 1999a; Walker et al 1999b), and in the ventroposterolateral nucleus of the thalamus, in which cannabinoids proved to be 10-fold more potent than morphine in wide dynamic range neurons mediating pain (Martin et al 1996). The ECS also mediates central stress-induced analgesia (Hohmann et al 2005), and is active in nociceptive spinal areas (Hohmann et al 1995; Richardson et al 1998a) including mechanisms of wind-up (Strangman and Walker 1999) and N-methyl-D-aspartate (NMDA) receptors (Richardson et al 1998b). It was recently demonstrated that cannabinoid agonists suppress the maintenance of vincristine-induced allodynia through activation of $CB_1$ and $CB_2$ receptors in the spinal cord (Rahn et al 2007). The ECS is also active peripherally (Richardson et al 1998c) where $CB_1$ stimulation reduces pain, inflammation and hyperalgesia. These mechanisms were also proven to include mediation of contact dermatitis via $CB_1$ and $CB_2$ with benefits of THC noted systemically and locally on inflammation and itch (Karsak et al 2007). Recent experiments in mice have even suggested the paramount importance of peripheral over central $CB_1$ receptors in nociception of pain (Agarwal et al 2007)

Cannabinoid agonists produce many effects beyond those mediated directly on receptors, including anti-inflammatory effects and interactions with various other neurotransmitter systems (previously reviewed (Russo 2006a)). Briefly stated, THC effects in serotonergic systems are widespread, including its ability to decrease 5-hydroxytryptamine (5-HT) release from platelets (Volfe et al 1985), increase its cerebral production and decrease synaptosomal uptake (Spadone 1991). THC may affect many mechanisms of the trigeminovascular system in migraine (Akerman et al 2003; Akerman et al 2004; Akerman et al 2007; Russo 1998; Russo 2001). Dopaminergic blocking actions of THC (Müller-Vahl et al 1999) may also contribute to analgesic benefits.

The glutamatergic system is integral to development and maintenance of neuropathic pain, and is responsible for generating secondary and tertiary hyperalgesia in migraine and fibromyalgia via NMDA mechanisms (Nicolodi et al 1998). Thus, it is important to note that cannabinoids presynaptically inhibit glutamate release (Shen et al 1996), THC produces 30%–40% reduction in NMDA responses, and THC is a neuroprotective antioxidant (Hampson et al 1998). Additionally, cannabinoids reduce hyperalgesia via inhibition of calcitonin gene-related peptide (Richardson et al 1998a). As for Substance P mechanisms, cannabinoids block capsaicin-induced hyperalgesia (Li et al 1999), and THC will do so at sub-psychoactive doses in experimental animals (Ko and Woods 1999). Among the noteworthy interactions with opiates and the endorphin/enkephalin system, THC has been shown to stimulate beta-endorphin production (Manzanares et al 1998), may allow opiate sparing in clinical application (Cichewicz et al 1999), prevents development of tolerance to and withdrawal from opiates (Cichewicz and Welch 2003), and rekindles opiate analgesia after a prior dosage has worn off (Cichewicz and McCarthy 2003). These are all promising attributes for an adjunctive agent in treatment of clinical chronic pain states.

The anti-inflammatory contributions of THC are also extensive, including inhibition of PGE-2 synthesis (Burstein et al 1973), decreased platelet aggregation (Schaefer et al 1979), and stimulation of lipooxygenase (Fimiani et al 1999). THC has twenty times the anti-inflammatory potency

of aspirin and twice that of hydrocortisone (Evans 1991), but in contrast to all nonsteroidal anti-inflammatory drugs (NSAIDs), demonstrates no cyclo-oxygenase (COX) inhibition at physiological concentrations (Stott et al 2005a).

Cannabidiol, a non-euphoriant phytocannabinoid common in certain strains, shares neuroprotective effects with THC, inhibits glutamate neurotoxicity, and displays antioxidant activity greater than ascorbic acid (vitamin C) or tocopherol (vitamin E) (Hampson et al 1998). While THC has no activity at vanilloid receptors, CBD, like AEA, is a $TRPV_1$ agonist that inhibits fatty acid amidohydrolase (FAAH), AEA's hydrolytic enzyme, and also weakly inhibits AEA reuptake (Bisogno et al 2001). These activities reinforce the conception of CBD as an endocannabinoid modulator, the first clinically available (Russo and Guy 2006). CBD additionally affects THC function by inhibiting first pass hepatic metabolism to the possibly more psychoactive 11-hydroxy-THC, prolonging its half-life, and reducing associated intoxication, panic, anxiety and tachycardia (Russo and Guy 2006). Additionally, CBD is able to inhibit tumor necrosis factor-alpha (TNF-α) in its own right in a rodent model of rheumatoid arthritis (Malfait et al 2000). At a time when great concern is accruing in relation to NSAIDs in relation to COX-1 inhibition (gastrointestinal ulcers and bleeding) and COX-2 inhibition (myocardial infarction and cerebrovascular accidents), CBD, like THC, inhibits neither enzyme at pharmacologically relevant doses (Stott et al 2005a). A new explanation of inflammatory and analgesic effects of CBD has recently come to light with the discovery that it is able to promote signaling of the adenosine receptor A2A by inhibiting the adenosine transporter (Carrier et al 2006).

Other "minor phytocannabinoids" in cannabis may also contribute relevant activity (McPartland and Russo 2001). Cannabichromene (CBC) is the third most prevalent cannabinoid in cannabis, and is also anti-inflammatory (Wirth et al 1980), and analgesic, if weaker than THC (Davis and Hatoum 1983). Cannabigerol (CBG) displays sub-micromolar affinity for $CB_1$ and $CB_2$ (Gauson et al 2007). It also exhibits GABA uptake inhibition to a greater extent than THC or CBD (Banerjee et al 1975), suggesting possible utilization as a muscle relaxant in spasticity. Furthermore, CBG has more potent analgesic, anti-erythema and lipooxygenase blocking activity than THC (Evans 1991), mechanisms that merit further investigation. It requires emphasis that drug stains of North American (ElSohly et al 2000; Mehmedic et al 2005), and European (King et al 2005) cannabis display relatively high concentrations of THC, but are virtually lacking in CBD or other phytocannabinoid content.

Cannabis terpenoids also display numerous attributes that may be germane to pain treatment (McPartland and Russo 2001). Myrcene is analgesic, and such activity, in contrast to cannabinoids, is blocked by naloxone (Rao et al 1990), suggesting an opioid-like mechanism. It also blocks inflammation via PGE-2 (Lorenzetti et al 1991). The cannabis sesquiterpenoid β-caryophyllene shows increasing promise in this regard. It is anti-inflammatory comparable to phenylbutazone via PGE-1 (Basile et al 1988), but simultaneously acts as a gastric cytoprotective (Tambe et al 1996). The analgesic attributes of β-caryophyllene are increasingly credible with the discovery that it is a selective $CB_2$ agonist (Gertsch et al 2007), with possibly broad clinical applications. α-Pinene also inhibits PGE-1 (Gil et al 1989), while linalool displays local anesthetic effects (Re et al 2000).

Cannabis flavonoids in whole cannabis extracts may also contribute useful activity (McPartland and Russo 2001). Apigenin inhibits TNF-α (Gerritsen et al 1995), a mechanism germane to multiple sclerosis and rheumatoid arthritis. Cannflavin A, a flavone unique to cannabis, inhibits PGE-2 thirty times more potently than aspirin (Barrett et al 1986), but has not been subsequently investigated.

Finally, β-sitosterol, a phytosterol found in cannabis, reduced topical inflammation 65% and chronic edema 41% in skin models (Gomez et al 1999).

## Available cannabinoid analgesic agents and those in development

Very few randomized controlled trials (RCTs) have been conducted using smoked cannabis (Campbell et al 2001) despite many anecdotal claims (Grinspoon and Bakalar 1997). One such study documented slight weight gain in HIV/AIDS subjects with no significant immunological sequelae (Abrams et al 2003). A recent brief trial of smoked cannabis (3.56% THC cigarettes 3 times daily) in HIV-associated neuropathy showed positive results on daily pain, hyperalgesia and 30% pain reduction (vs 15% in placebo) in 50 subjects over a treatment course of only 5 days (Abrams et al 2007) (Table 1). This short clinical trial also demonstrated prominent adverse events associated with intoxication. In Canada, 21 subjects with chronic pain sequentially smoked single inhalations of 25 mg of cannabis (0, 2.5, 6.0, 9.5% THC) via a pipe three times a day for 5 days to assess effects on pain (Ware et al 2007) with results the authors termed "modest": no changes were observed in acute neuropathic pain scores, and a very low number of subjects noted 30% pain relief at the end of the study (Table 1). Even after political and legal considerations, it remains extremely unlikely that crude cannabis could

**Table 1** Results RCTs of cannabinoids in treatment of pain syndromes ()

| Drug | Subject number N = | RCT indication | Trial duration | Results/Reference |
|---|---|---|---|---|
| Ajulemic Acid | 21 | Neuropathic pain | 7 day crossover | VAS improved over placebo ($p = 0.02$) (Karst et al 2003) |
| Cannabis, smoked | 50 | HIV neuropathy | 5 days | Decreased daily pain ($p = 0.03$) and hyperalgesia ($p = 0.05$), 52% with >30% pain reduction vs placebo ($p = 0.04$) (Abrams et al 2007) |
| Cannabis, Smoked | 21 | Chronic neuropathic pain | 5 days | No acute benefit on pain, average daily pain lower on high THC cannabis vs placebo ($p = 0.02$ ) (Ware et al 2007) |
| Cannador | 419 | Pain due to spasm in MS | 15 weeks | Improvement over placebo in subjective pain associated with spasm ($p = 0.003$) (Zajicek et al 2003) |
| Cannador | 65 | Post-herpetic neuralgia | 4 weeks | No benefit observed (Ernst et al 2005) |
| Cannador | 30 | Post-operative pain | Single doses, daily | Decreasing pain intensity with increased dose ($p = 0.01$)(Holdcroft et al 2006) |
| Marinol | 24 | Neuropathic pain in MS | 15–21 days, crossover | Median numerical pain ($p = 0.02$), median pain relief improved ($p = 0.035$) over placebo (Svendsen et al 2004) |
| Marinol | 40 | Post-operative pain | Single dose | No benefit observed over placebo (Buggy et al 2003) |
| Nabilone | 41 | Post-operative pain | 3 doses in 24 hours | NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg (Beaulieu 2006) |
| Sativex | 20 | Neurogenic pain | Series of 2-week N-of-1 crossover blocks | Improvement with Tetranabinex and Sativex on VAS pain vs placebo ($p < 0.05$), symptom control best with Sativex ($p < 0.0001$) (Wade et al 2003) |
| Sativex | 24 | Chronic intractable pain | 12 weeks, series of N-of-1 crossover blocks | VAS pain improved over placebo ($p < 0.001$) especially in MS ($p < 0.0042$) (Notcutt et al 2004) |
| Sativex | 48 | Brachial plexus avulsion | 6 weeks in 3 two-week crossover blocks | Benefits noted in Box Scale-11 pain scores with Tetranabinex ($p = 0.002$) and Sativex ($p = 0.005$) over placebo (Berman et al 2004) |
| Sativex | 66 | Central neuropathic pain in MS | 5 weeks | NRS analgesia improved over placebo ($p = 0.009$) (Rog et al 2005) |
| Sativex | 125 | Peripheral neuropathic pain | 5 weeks | Improvements in NRS pain levels ($p = 0.004$), dynamic allodynia ($p = 0.042$), and punctuate allodynia ($p = 0.021$) vs placebo (Nurmikko et al 2007) |
| Sativex | 56 | Rheumatoid arthritis | Nocturnal dosing for 5 weeks | Improvements over placebo morning pain on movement ($p = 0.044$), morning pain at rest ($p = 0.018$), DAS-28 |

(*Continued*)

**Table 1** (*Continued*)

| Drug | Subject number | RCT indication | Trial duration | Results/Reference |
|---|---|---|---|---|
| | | | | (p = 0.002), and SF-MPQ pain at present (p = 0.016) (Blake et al 2006) |
| Sativex | 117 | Pain after spinal injury | 10 days | NSD in NRS pain socres, but improved Brief Pain Inventory (p = 0.032), and Patients Global Impression of Change (p = 0.001) (unpublished) |
| Sativex | 177 | Intractable cancer pain | 2 weeks | Improvements in NRS analgesia vs placebo (p = 0.0142), Tetranabinex NSD (Johnson and Potts 2005) |
| Sativex | 135 | Intractable lower urinary tract symptoms in MS | 8 weeks | Improved bladder severity symptoms including pain over placebo (p = 0.001) (unpublished) |

**Abbreviations:** MS, multiple sclerosis; NRS, numerical rating scale; NSD, no significant difference; RCTs, randomized clinical trials; VAS, visual analogue pain scales.

ever be approved by the FDA as a prescription medicine as outlined in the FDA Botanical Guidance document (Food and Drug Administration 2004; Russo 2006b), due to a lack of rigorous standardization of the drug, an absence of Phase III clinical trials, and pulmonary sequelae (bronchial irritation and cough) associated with smoking (Tashkin 2005). Although cannabis vaporizers reduce potentially carcinogenic polyaromatic hydrocarbons, they have not been totally eliminated by this technology (Gieringer et al 2004; Hazekamp et al 2006).

Oral dronabinol (THC) is marketed in synthetic form as Marinol® (Solvay Pharmaceuticals) in various countries, and was approved in the USA for nausea associated with chemotherapy in 1985, and in 1992 for appetite stimulation in HIV/AIDS. Oral dronabinol's expense, variability of action, and attendant intoxication and dysphoria have limited its adoption by clinicians (Calhoun et al 1998). Two open label studies in France of oral dronabinol for chronic neuropathic pain in 7 subjects (Clermont-Gnamien et al 2002) and 8 subjects (Attal et al 2004), respectively, failed to show significant benefit on pain or other parameters, and showed adverse event frequently requiring discontinuation with doses averaging 15–16.6 mg THC. Dronabinol did demonstrate positive results in a clinical trial of multiple sclerosis pain in two measures (Svendsen et al 2004), but negative results in post-operative pain (Buggy et al 2003) (Table 1). Another uncontrolled case report in three subjects noted relief of intractable pruritus associated with cholestatic jaundice employing oral dronabinol (Neff et al 2002). Some authors have noted patient preference for whole cannabis preparations over oral THC (Joy et al 1999), and the contribution of other components beyond THC to therapeutic benefits (McPartland and Russo 2001). Inhaled THC leads to peak plasma concentration within 3–10 minutes, followed by a rapid fall while levels of intoxication are still rising, and with systemic bioavailability of 10%–35% (Grotenhermen 2004). THC absorption orally is slow and erratic with peak serum levels in 45–120 minutes or longer. Systemic bioavailability is also quite low due to rapid hepatic metabolism on first pass to 11-hydroxy-THC. A rectal suppository of THC-hemisuccinate is under investigation (Broom et al 2001), as are transdermal delivery techniques (Challapalli and Stinchcomb 2002). The terminal half-life of THC is quite prolonged due to storage in body lipids (Grotenhermen 2004).

Nabilone (Cesamet) (Figure 1), is a synthetic dimethylheptyl analogue of THC (British Medical Association 1997) that displays greater potency and prolonged half-life. Serum levels peak in 1–4 hours (Lemberger et al 1982). It was also primarily developed as an anti-emetic in chemotherapy, and was recently re-approved for this indication in the USA. Prior case reports have noted analgesic effects in case reports in neuropathic pain (Notcutt et al 1997) and other pain disorders (Berlach et al 2006). Sedation and dysphoria were prominent sequelae. An RCT of nabilone in 41 post-operative subjects actually documented exacerbation of pain scores after thrice daily dosing (Beaulieu 2006) (Table 1). An abstract of a study

of 82 cancer patients on nabilone claimed improvement in pain levels after varying periods of follow-up compared to patients treated without this agent (Maida 2007). However, 17 subjects dropped out, and the study was neither randomized nor controlled, and therefore is not included in Table 1.

Ajulemic acid (CT3, IP-751) (Figure 1), another synthetic dimethylheptyl analogue, was employed in a Phase II RCT in 21 subjects with improvement in peripheral neuropathic pain (Karst et al 2003) (Table 1). Part of its analgesic activity may relate to binding to intracellular peroxisome proliferator-activator receptor gamma (Liu et al 2003). Peak plasma concentrations have generally been attained in 1–2 hours, but with delays up to 4–5 hours is some subjects (Karst et al 2003). Debate surrounds the degree of psychoactivity associated with the drug (Dyson et al 2005). Current research is confined to the indication of interstitial cystitis.

Cannador® (IKF-Berlin) is a cannabis extract administered in oral capsules, with differing figures as to THC:CBD ratios (reviewed in (Russo and Guy 2006)), generally approximately 2:1. Two pharmacokinetic studies on possibly related material have been reported (Nadulski et al 2005a; Nadulski et al 2005b). In a Phase III RCT employing Cannador in spasticity in multiple sclerosis (MS) (CAMS) (Zajicek et al 2003) (Table 1), no improvement was noted in the Ashworth Scale, but benefit was observed in spasm-associated pain on subjective measures. Both Marinol and Cannador produced reductions in pain scores in long-term follow-up (Zajicek et al 2005). Cannador was assayed in postherpetic neuralgia in 65 subjects with no observed benefit (Ernst et al 2005) (Table 1), and in 30 post-operative pain subjects (CANPOP) without opiates, with slight benefits, but prominent psychoactive sequelae (Holdcroft et al 2006) (Table 1).

Sativex® (GW Pharmaceuticals) is an oromucosal whole cannabis-based spray combining a $CB_1$ partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring (McPartland and Russo 2001; Russo and Guy 2006). It was approved by Health Canada in June 2005 for prescription for central neuropathic pain in multiple sclerosis, and in August 2007, it was additionally approved for treatment of cancer pain unresponsive to optimized opioid therapy. Sativex is a highly standardized pharmaceutical product derived from two *Cannabis sativa* chemovars following Good Agricultural Practice (GAP) (de Meijer 2004), yielding Tetranabinex® (predominantly-THC extract) and Nabidiolex® (predominantly-CBD extract) in a 1:1 ratio. Each 100 μL pump-action oromucosal Sativex spray actuation provides 2.7 mg of THC and 2.5 mg of CBD. Pharmacokinetic data are available, and indicate plasma half lives of 85 minutes for THC, 130 minutes for 11-hydroxy-THC and 100 minutes for CBD (Guy and Robson 2003). Sativex effects commence in 15–40 minutes, an interval that permits symptomatic dose titration. A very favorable adverse event profile has been observed in over 2500 patient years of exposure in over 2000 experimental subjects. Patients most often ascertain an individual stable dosage within 7–10 days that provides therapeutic relief without unwanted psychotropic effects (often in the range of 8–10 sprays per day). In all RCTs, Sativex was adjunctively added to optimal drug regimens in subjects with intractable symptoms, those often termed "untreatable." Sativex is also available by named patient prescription in the UK and the Catalonia region of Spain. An Investigational New Drug (IND) application to study Sativex in advanced clinical trials in the USA was approved by the FDA in January 2006 in patients with intractable cancer pain.

The clinical trials performed with Sativex have recently been assessed in two independent review articles (Barnes 2006; Pérez 2006). In a Phase II clinical trial in 20 patients with neurogenic symptoms (Wade et al 2003), Tetranabinex, Nabidiolex, and Sativex were tested in a double-blind RCT vs placebo (Table 1). Significant improvement was seen with both Tetranabinex and Sativex on pain (especially neuropathic), but post-hoc analysis showed symptom control was best with Sativex ($p < 0.0001$), with less intoxication than with THC-predominant extract.

In a Phase II double-blind crossover study of intractable chronic pain (Notcutt et al 2004) in 24 subjects, visual analogue scales (VAS) were 5.9 for placebo, 5.45 for Nabidiolex, 4.63 for Tetranabinex and 4.4 for Sativex extracts ($p < 0.001$). Sativex produced best results for pain in MS subjects ($p < 0.0042$) (Table 1).

In a Phase III study of pain associated due to brachial plexus avulsion (N = 48) (Berman et al 2004), fairly comparable benefits were noted in Box Scale-11 pain scores with Tetranabinex and Sativex extracts (Table 1).

In a controlled double-blind RCT of central neuropathic pain, 66 MS subjects showed mean Numerical Rating Scale (NRS) analgesia favoring Sativex over placebo (Rog et al 2005) (Table 1).

In a Phase III double-blind, placebo-controlled trial (N = 125) of peripheral neuropathic pain with allodynia (Nurmikko et al 2007), Sativex produced highly statistically significant improvements in pain levels, dynamic and punctate allodynia (Table 1).

In a SAFEX study of Phase III double-blind RCT in 160 subjects with various symptoms of MS (Wade et al 2004), 137 patients elected to continue on Sativex after the initial study (Wade et al 2006). Rapid declines were noted in the first twelve weeks in pain VAS (N = 47) with slower sustained improvements for more than one year. During that time, there was no escalation of dose indicating an absence of tolerance to the preparation. Similarly, no withdrawal effects were noted in a subset of patients who voluntarily stopped the medicine abruptly. Upon resumption, benefits resumed at the prior established dosages.

In a Phase II double-blind, randomized, placebo-controlled, 5-week study of 56 rheumatoid arthritis patients with Sativex (Blake et al 2006), employed nocturnal treatment only to a maximum of 6 sprays per evening (16.2 mg THC + 15 mg CBD). In the final treatment week, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain at present all favored Sativex over placebo (Table 1).

Results of a Phase III study (N = 177) comparing Sativex, THC-predominant extract and placebo in intractable pain due to cancer unresponsive to opiates (Johnson and Potts 2005) demonstrated that Sativex produced highly statistically significant improvements in analgesia (Table 1), while the THC-predominant extract failed to produce statistical demarcation from placebo, suggesting the presence of CBD in the Sativex preparation was crucial to attain significant pain relief.

In a study of spinal injury pain, NRS of pain were not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were clearly positive (Table 1). Finally, in an RCT of intractable lower urinary tract symptoms in MS, accompanying pain in affected patients was prominently alleviated (Table 1).

Highly statistically significant improvements have been observed in sleep parameters in virtually all RCTs performed with Sativex in chronic pain conditions leading to reduced "symptomatic insomnia" due to symptom reduction rather than sedative effects (Russo et al 2007).

Common adverse events (AE) of Sativex acutely in RCTs have included complaints of bad taste, oral stinging, dry mouth, dizziness, nausea or fatigue, but do not generally necessitate discontinuation, and prove less common over time. While there have been no head-to-head comparative RCTs of Sativex with other cannabinoid agents, certain contrasts can be drawn. Sativex (Rog et al 2005) and Marinol (Svendsen et al 2004) have both been examined in treatment of central neuropathic pain in MS, with comparable results (Table 1). However, adverse events were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher due to the presence of accompanying CBD (Russo 2006b; Russo and Guy 2006).

Similarly, while Sativex and smoked cannabis have not been employed in the same clinical trial, comparisons of side effect profiles can be made on the basis of SAFEX studies of Sativex for over a year and up to several years in MS and other types of neuropathic pain (Russo 2006b; Wade et al 2006), and government-approved research programs employing standardized herbal cannabis from Canada for chronic pain (Lynch et al 2006) and the Netherlands for general conditions (Janse et al 2004; Gorter et al 2005) over a period of several months or more. As is evident in Figure 2 (Figure 2), all adverse events are more frequently reported with herbal cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex (see (Russo 2006b) for additional discussion).

## Practical issues with cannabinoid medicines

Phytocannabinoids are lipid soluble with slow and erratic oral absorption. While cannabis users claim that the smoking of cannabis allows easy dose titration as a function of rapid onset, high serum levels in a short interval inevitably result. This quick onset is desirable for recreational purposes, wherein intoxication is the ultimate goal, but aside from paroxysmal disorders (eg, episodic trigeminal neuralgia or cluster headache attack), such rapid onset of activity is not usually necessary for therapeutic purposes in chronic pain states. As more thoroughly reviewed elsewhere (Russo 2006b), cannabis smoking produces peak levels of serum THC above 140 ng/mL (Grotenhermen 2003; Huestis et al 1992), while comparable amounts of THC in Sativex administered oromucosally remained below 2 ng/mL (Guy and Robson 2003).

The vast majority of subjects in Sativex clinical trials do not experience psychotropic effects outside of initial dose titration intervals (Figure 2) and most often report subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 (Wade et al 2006). Thus, it is now longer tenable to claim that psychoactive effects are a necessary prerequisite to symptom relief in the therapeutic setting with a standardized intermediate onset cannabis-based preparation. Intoxication has remained a persistent issue in Marinol usage (Calhoun et al 1998), in contrast.

Recent controversies have arisen in relation to non-steroidal anti-inflammatory drugs (NSAID), with concerns

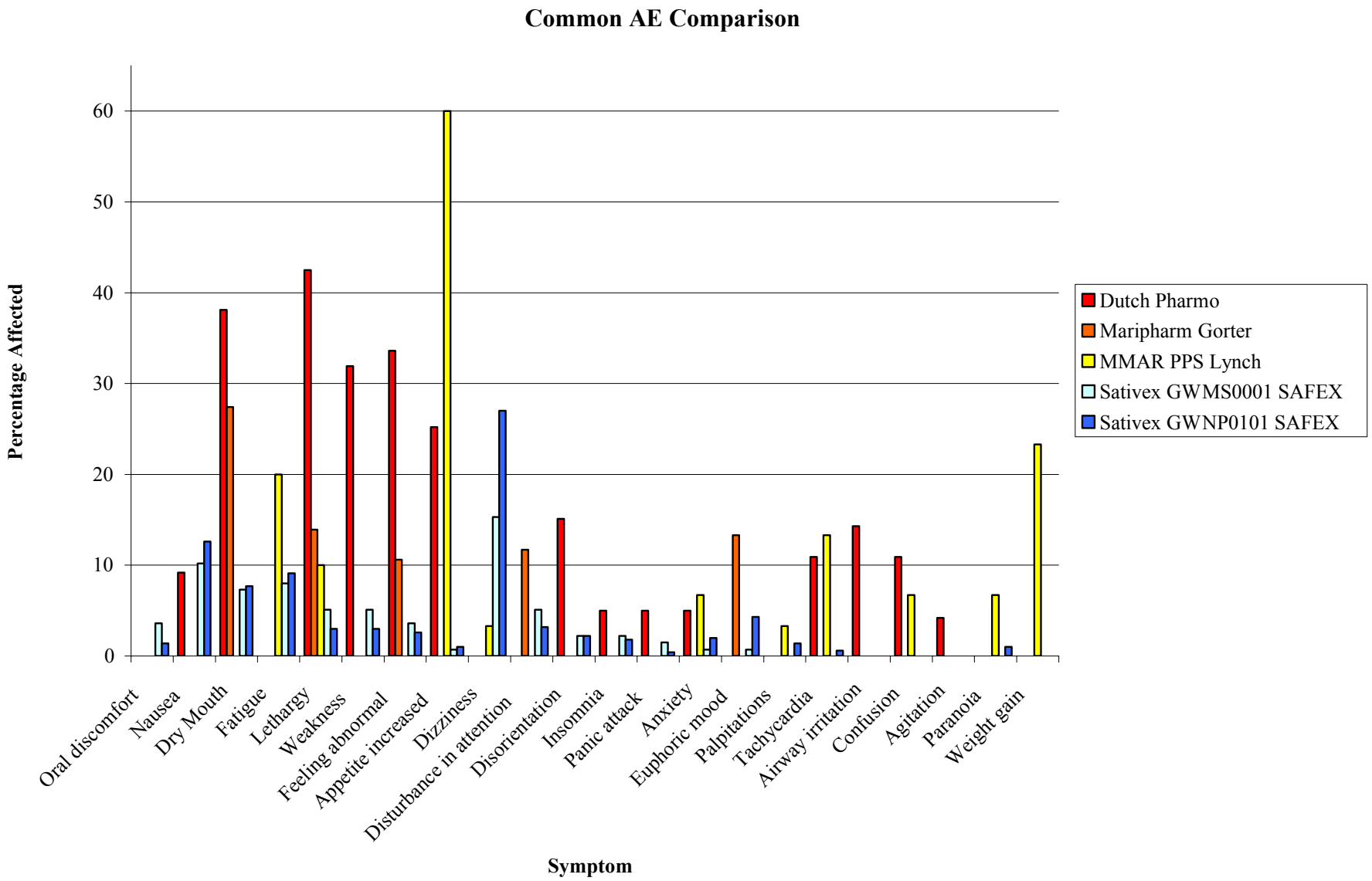



**Figure 2** Comparison of adverse events (AE) encountered with long term therapeutic use of herbal cannabis in the Netherlands (Janse et al 2004; Gorter et al 2005) and Canada (Lynch et al 2006), vs that observed in safety-extension (SAFEX) studies of Sativex oromucosal spray (Russo 2006; Wade et al 2006).

that COX-1 agents may provoke gastrointestinal ulceration and bleeding, and COX-2 drugs may increase incidents of myocardial infarction and cerebrovascular accidents (Fitzgerald 2004; Topol 2004). In contrast, neither THC nor CBD produce significant COX inhibition at normal dosage levels (Stott et al 2005a).

Frequent questions have been raised as to whether psychoactive drugs may be adequately blinded (masked) in randomized clinical trials. Internal review and outside analysis have confirmed that blinding in Sativex spasticity studies has been effective (Clark and Altman 2006; Wright 2005). Sativex and its placebo are prepared to appear identical in taste and color. About half of clinical trial subjects reported previous cannabis exposure, but results of two studies (Rog et al 2005; Nurmikko et al 2007) support the fact that cannabis-experienced and naïve patients were identical in observed efficacy and adverse event reporting

Great public concern attends recreational cannabis usage and risks of dependency. The addictive potential of a drug is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal and dependency. Drug abuse liability (DAL) is also assessed by examining a drug's rates of abuse and diversion. US Congress placed cannabis in Schedule I of the Controlled Substances Act in 1970, with drugs categorized as addictive, dangerous, possessing severe abuse potential and no recognized medical value. Marinol was placed in Schedule II, the category for drugs with high abuse potential and liability to produce dependency, but certain recognized medical uses, after its FDA approval in 1985. Marinol was reassigned to Schedule III in 1999, a category denoting a lesser potential for abuse or lower dependency risk after documentation that little abuse or diversion (Calhoun et al 1998) had occurred. Nabilone was placed and has remained in Schedule II since 1985.

The degree to which a drug is reinforcing is determined partly by the by the rate of its delivery to the brain (Samaha and Robinson 2005). Sativex has effect onset in 15–40 minutes, peaking in a few hours, quite a bit slower than drugs of high abuse potential. It has been claimed that inclusion of CBD diminishes psychoactive effects of THC, and may lower potential drug abuse liability of the preparation (see Russo (2006b)) for discussion). Prior studies from Sativex clinical trials do not support the presence reinforcement or euphoria as problems in administration (Wade et al 2006).

Certain facets of acute cannabinoid exposure, including tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, intraocular pressure decreases, etc. are subject to rapid tachyphylaxis upon continued administration (Jones et al 1976). No dose tolerance to the therapeutic effects of Sativex has been observed in clinical trials in over 1500 patient-years of administration. Additionally, therapeutic efficacy has been sustained for several years in a wide variety of symptoms; SAFEX studies in MS and peripheral neuropathic pain, confirm that Sativex doses remain stable or even decreased after prolonged usage (Wade et al 2006), with maintenance of therapeutic benefit and even continued improvement.

Debate continues as to the existence of a clinically significant cannabis withdrawal syndrome with proponents (Budney et al 2004), and questioners (Smith 2002). While withdrawal effects have been reported in recreational cannabis smokers (Solowij et al 2002), 24 volunteers with MS who abruptly stopped Sativex after more than a year of continuous usage displayed no withdrawal symptoms meeting Budney's criteria. While symptoms recurred after 7–10 days of abstinence from Sativex, prior levels of symptom control were readily re-established upon re-titration of the agent (Wade et al 2006).

Overall, Sativex appears to pose less risk of dependency than smoked cannabis based on its slower onset, lower dosage utilized in therapy, almost total absence of intoxication in regular usage, and minimal withdrawal symptomatology even after chronic administration. No known abuse or diversion incidents have been reported with Sativex to date (as of November 2007). Sativex is expected to be placed in Schedule IV of the Misuse of Drugs Act in the United Kingdom once approved.

Cognitive effects of cannabis have been reviewed (Russo et al 2002; Fride and Russo 2006), but less study has occurred in therapeutic contexts. Effects of chronic heavy recreational cannabis usage on memory abate without sequelae after a few weeks of abstinence (Pope et al 2001). Studies of components of the Halstead-Reitan battery with Sativex in neuropathic pain with allodynia have revealed no changes vs placebo (Nurmikko et al 2007), and in central neuropathic pain in MS (Rog et al 2005), 4 of 5 tests showed no significant differences. While the Selective Reminding Test did not change significantly on Sativex, placebo patients displayed unexpected improvement.

Slight improvements were observed in Hospital Anxiety and Depression Scales depression and anxiety scores were noted with Sativex in MS patients with central neuropathic pain (Rog et al 2005), although not quite statistically significant. No long-term mood disorders have been associated with Sativex administration.

Debate continues with regard to the relationship between cannabis usage and schizophrenia (reviewed (Fride and

Russo 2006)). An etiological relationship is not supported by epidemiological data (Degenhardt et al 2003), but if present, should bear relation to dose and length of high exposure. It is likely that lower serum levels of Sativex in therapeutic usage, in conjunction with anti-psychotic properties of CBD (Zuardi and Guimaraes 1997), would minimize risks. Children and adolescents have been excluded from Sativex RCTs to date. SAFEX studies of Sativex have yielded few incidents of thought disorder, paranoia or related complaints.

Adverse effects of cannabinoids on immune function have been observed in experimental animals at doses 50–100 times the psychoactive level (Cabral 2001). In four patients using herbal cannabis therapeutically for over 20 years, no abnormalities were observed in leukocyte, CD4 or CD8 cell counts (Russo et al 2002). Investigation of MS patients on Cannador revealed no major immune changes (Katona et al 2005), and similarly, none occurred with smoked cannabis in a short-term study of HIV patients (Abrams et al 2003). Hematological measures have been normal in all Sativex RCTs without clinical signs of immune dysfunction.

Concerns are frequently noted with new drug-drug interactions, but few have resulted in Sativex RCTs despite its adjunctive use with opiates, many other psychoactive analgesic, antidepressant and anticonvulsant drugs (Russo 2006a), possibly due to CBD ability to counteract sedative effects of THC (Nicholson et al 2004). No effects of THC extract, CBD extract or Sativex were observed in a study of effects on the hepatic cytochrome P450 complex (Stott et al 2005b). On additional study, at 314 ng/ml cannabinoid concentration, Sativex and components produced no significant induction on human CYP450 (Stott et al 2007). Thus, Sativex should be safe to use in conjunction with other drugs metabolized via this pathway.

The Marinol patient monograph cautions that patients should not drive, operate machinery or engage in hazardous activities until accustomed to the drug's effects (http://www.solvaypharmaceuticals-us.com/static/wma/pdf/1/3/1/9/Marinol5000124ERev52003.pdf ). The Sativex product monograph in Canada (http://www.bayerhealth.ca/display.cfm?Object_ID=272&Article_ID=121&expandMenu_ID=53&prevSubItem=5_52 ) suggests that patients taking it should not drive automobiles. Given that THC is the most active component affecting such abilities, and the low serum levels produced in Sativex therapy (vide supra), it would be logical that that patients may be able to safely engage in such activities after early dose titration and according to individual circumstances, much as suggested for oral dronabinol. This is particularly the case in view of a report by an expert panel (Grotenhermen et al 2005) that comprehensively analyzed cannabinoids and driving. It suggested scientific standards such as roadside sobriety tests, and THC serum levels of 7–10 ng/mL or less, as reasonable approaches to determine relative impairment. No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/mL of THC. Prior studies document that 4 rapid oromucosal sprays of Sativex (greater than the average single dose employed in therapy) produced serum levels well below this threshold (Russo 2006b). Sativex is now well established as a cannabinoid agent with minimal psychotropic effect.

Cannabinoids may offer significant "side benefits" beyond analgesia. These include anti-emetic effects, well established with THC, but additionally demonstrated for CBD (Pertwee 2005), the ability of THC and CBD to produce apoptosis in malignant cells and inhibit cancer-induced angiogenesis (Kogan 2005; Ligresti et al 2006), as well as the neuroprotective antioxidant properties of the two substances (Hampson et al 1998), and improvements in symptomatic insomnia (Russo et al 2007).

The degree to which cannabinoid analgesics will be adopted into adjunctive pain management practices currently remains to be determined. Data on Sativex use in Canada for the last reported 6-month period (January-July 2007) indicated that 81% of prescriptions issued for patients in that interval were refills (data on file, from Brogan Inc Rx Dynamics), thus indicating in some degree an acceptance of, and a desire to, continue such treatment. Given their multi-modality effects upon various nociceptive pathways, their adjunctive side benefits, the efficacy and safety profiles to date of specific preparations in advanced clinical trials, and the complementary mechanisms and advantages of their combination with opioid therapy, the future for cannabinoid therapeutics appears very bright, indeed.

## References

ABC News, USA Today, Stanford Medical Center Poll. 2005. Broad experience with pain sparks search for relief [online]. URL: http://abcnews.go.com/images/Politics/979a1TheFightAgainstPain.pdf.

Abrams DI, Hilton JF, Leiser RJ, et al. 2003. Short-term effects of cannabinoids in patients with HIV-1 infection. A randomized, placbo-controlled clinical trial. *Ann Intern Med*, 139:258–66.

Abrams DI, Jay CA, Shade SB, et al. 2007. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*, 68:515–21.

Agarwal N, Pacher P, Tegeder I, et al. 2007. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. *Nat Neurosci*, 10:870–9.

Akerman S, Holland PR, Goadsby PJ. 2007. Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. *J Pharmacol Exp Ther*, 320:64–71.

Akerman S, Kaube H, Goadsby PJ. 2003. Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. *J Pharmacol Exp Ther*, 309 :56–63.

Akerman S, Kaube H, Goadsby PJ. 2004. Anandamide acts as a vasodilator of dural blood vessels in vivo by activating TRPV1 receptors. *Br J Pharmacol*, 142:1354–60.

Attal N, Brasseur L, Guirimand D, et al. 2004. Are oral cannabinoids safe and effective in refractory neuropathic pain? *Eur J Pain*, 8:173–7.

Banerjee SP, Snyder SH, Mechoulam R. 1975. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. *J Pharmacol Exp Ther*, 194:74–81.

Barnes MP. 2006. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opin Pharmacother*, 7:607–15.

Barrett ML, Scutt AM, Evans FJ. 1986. Cannflavin A and B, prenylated flavones from *Cannabis sativa* L. *Experientia*, 42:452–3.

Basile AC, Sertie JA, Freitas PC, et al. 1988. Anti-inflammatory activity of oleoresin from Brazilian Copaifera. *J Ethnopharmacol*, 22:101–9.

Beaulieu P. 2006. Effects of nabilone, a synthetic cannabinoid, on postoperative pain: [Les effets de la nabilone, un cannabinoide synthetique, sur la douleur postoperatoire]. *Can J Anaesth*, 53:769–75.

Berlach DM, Shir Y, Ware MA. 2006. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Med*, 7:25–9.

Berman JS, Symonds C, Birch R. 2004. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain*, 112:299–306.

Bisogno T, Hanus L, De Petrocellis L, et al. 2001. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol*, 134:845–52.

Blake DR, Robson P, Ho M, Jubb RW, et al. 2006. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)*, 45:50–2.

British Medical Association. 1997. Therapeutic uses of cannabis. Amsterdam: Harwood Academic Publishers. 142 p.

Broom SL, Sufka KJ, Elsohly MA, et al. 2001. Analgesic and reinforcing proerties of delta9-THC-hemisuccinate in adjuvant-arthritic rats. *Journal of Cannabis Therapeutics*, 1:171–82.

Budney AJ, Hughes JR, Moore BA, et al. 2004. Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry*, 161:1967–77.

Buggy DJ, Toogood L, Maric S, et al. 2003. Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain*, 106:169–72.

Burstein S, Levin E, Varanelli C. 1973. Prostaglandins and cannabis. II. Inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochem Pharmacol*, 22:2905–10.

Cabral G. 2001. Immune system. In: Russo EB, Grotenhermen F eds. Cannabis and cannabinoids: Pharmacology, toxicology and therapeutic potential. Binghamton, NY: Haworth Press. p 279–87.

Calhoun SR, Galloway GP, Smith DE. 1998. Abuse potential of dronabinol (Marinol). *J Psychoactive Drugs*, 30:187–96.

Campbell FA, Tramber MR, Carroll D, et al. 2001. Are cannabinoids an effective and safe option in the management of pain? A qualitative systematic review. *BMJ*, 323:1–6.

Carrier EJ, Auchampach JA, Hillard CJ. 2006. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci USA*, 103:7895–900.

Challapalli PV, Stinchcomb AL. 2002. In vitro experiment optimization for measuring tetrahydrocannabinol skin permeation. *Int J Pharm*, 241:329–39.

Cichewicz DL, Martin ZL, Smith FL, et al. 1999. Enhancement of mu opioid antinociception by oral delta9-tetrahydrocannabinol: Dose-response analysis and receptor identification. *J Pharmacol Exp Ther*, 289:859–67.

Cichewicz DL, McCarthy EA. 2003. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther*, 304:1010–5.

Cichewicz DL, Welch SP. 2003. Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral Delta 9-tetrahydrocannabinol. *J Pharmacol Exp Ther*, 305:812–7.

Clark P, Altman D. 2006. Assessment of blinding in Phase III Sativex spasticity studies. . GW Pharmaceuticals. 56 p.

Clermont-Gnamien S, Atlani S, Attal N, et al. 2002. Utilisation thérapeutique du delta-9-tétrahydrocannabinol (dronabinol) dans les douleurs neuropathiques réfractaires. [The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain]. *Presse Med*, 31(39 Pt 1):1840–5.

Davis WM, Hatoum NS. 1983. Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. *Gen Pharmacol*, 14:247–52.

de Meijer E. 2004. The breeding of cannabis cultivars for pharmaceutical end uses. In: Guy GW, Whittle BA, Robson P eds. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press. p 55–70.

Degenhardt L, Hall W, Lynskey M. 2003. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend*, 71:37–48.

Devane WA, Hanus L, Breuer A, et al. 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, 258:1946–9.

Di Marzo V, Melck D, Bisogno T, et al. 1998. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci*, 21:521–8.

Dogrul A, Gul H, Akar A, et al. 2003. Topical cannabinoid antinociception: synergy with spinal sites. *Pain*, 105:11–6.

Dyson A, Peacock M, Chen A, et al. 2005. Antihyperalgesic properties of the cannabinoid CT-3 in chronic neuropathic and inflammatory pain states in the rat. *Pain*, 116:129–37.

ElSohly MA, Ross SA, Mehmedic Z, et al. 2000. Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980–1997. *J Forensic Sci*, 45:24–30.

Ernst G, Denke C, Reif M, et al. 2005. Standardized cannabis extract in the treatment of postherpetic neuralgia: a randomized, double-blind, placebo-controlled cross-over study; 2005 September 9; Leiden, Netherlands. International Association for Cannabis as Medicine.

Evans FJ. 1991. Cannabinoids: The separation of central from peripheral effects on a structural basis. *Planta Med*, 57:S60–7.

Fimiani C, Liberty T, Aquirre AJ, et al. 1999. Opiate, cannabinoid, and eicosanoid signaling converges on common intracellular pathways nitric oxide coupling. *Prostaglandins Other Lipid Mediat*, 57:23–34.

Fishman SM. 2006. Pain and politics: DEA, Congress, and the courts, oh my! *Pain Med*, 7:87–8.

Fitzgerald GA. 2004. Coxibs and cardiovascular disease. *N Engl J Med*, 351:1709–11.

Food and Drug Administration. 2004. Guidance for industry: Botanical drug products. In: Services UDoHaH, ed. US Government. p 48.

Fox A, Kesingland A, Gentry C, et al. 2001. The role of central and peripheral Cannabinoid1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. *Pain*, 92:91–100.

Fride E, Russo EB. 2006. Neuropsychiatry: Schizophrenia, depression, and anxiety. In: Onaivi E, Sugiura T, Di Marzo V eds. Endocannabinoids: The brain and body's marijuana and beyond. Boca Raton, FL: Taylor and Francis. p 371–82.

Frondini C, Lanfranchi G, Minardi M, et al. 2007. Affective, behavior and cognitive disorders in the elderly with chronic musculoskelatal pain: the impact on an aging population. *Arch Gerontol Geriatr*, 44(Suppl 1):167–71.

Gaoni Y, Mechoulam R. 1964. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc*, 86:1646–7.

Gauson LA, Stevenson LA, Thomas A, et al. 2007. Cannabigerol behaves as a partial agonist at both CB1 and CB2 receptors. 17th Annual Symposium on the Cannabinoids. Saint-Sauveur, Quebec, Canada: International Cannabinoid Research Society. p 206.

Gerritsen ME, Carley WW, Ranges GE, et al. 1995. Flavonoids inhibit cytokine-induced endothelial cell adhesion protein gene expression. *Am J Pathol*, 147:278–92.

Gertsch J, Raduner S, Leonti M, et al. 2007. Screening of plant extracts for new CB2-selective agonists revewals new players in *Cannabis sativa*. 17th Annual Symposium on the Cannabinoids. Saint-Sauveur, Quebec, Canada: International Cannabinoid Research Society. p 213.

Gibson SJ. 2007. IASP global year against pain in older persons: highlighting the current status and future perspectives in geriatric pain. *Expert Rev Neurother*, 7:627–35.

Gieringer D, St. Laurent J, Goodrich S. 2004. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. *Journal of Cannabis Therapeutics*, 4:7–27.

Gil ML, Jimenez J, Ocete MA, et al. 1989. Comparative study of different essential oils of Bupleurum gibraltaricum Lamarck. *Pharmazie*, 44:284–7.

Gomez MA, Saenz MT, Garcia MD, et al. 1999. Study of the topical anti-inflammatory activity of Achillea ageratum on chronic and acute inflammation models. *Z Naturforsch [C]*, 54:937–41.

Gorter RW, Butorac M, Cobian EP, et al. 2005. Medical use of cannabis in the Netherlands. *Neurology*, 64:917–9.

Grinspoon L, Bakalar JB. 1997. Marihuana, the forbidden medicine. New Haven: Yale University Press. xv, 296 p.

Grotenhermen F. 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*, 42:327–60.

Grotenhermen F. 2004. Cannabinoids for therapeutic use: designing systems to increase efficacy and reliability. *American Journal of Drug Delivery*, 2:229–40.

Grotenhermen F, Leson G, Berghaus G, et al. 2005. Developing science-based per se limits for driving under the influence of cannabis (DUIC). Findings and recommendations by an expert panel. Hürth, Germany: Nova- Institut. 49 p.

Guy GW, Robson P. 2003. A Phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK02125). *Journal of Cannabis Therapeutics*, 3:121–52.

Hampson AJ, Grimaldi M, Axelrod J, et al. 1998. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA*, 95:8268–73.

Hazekamp A, Ruhaak R, Zuurman L, et al. 2006. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci*, 95:1308–17.

Herkenham M, Lynn AB, Little MD, et al. 1990. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci USA*, 87:1932–6.

Hohmann AG, Briley EM, Herkenham M. 1999. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Res*, 822:17–25.

Hohmann AG, Martin WJ, Tsou K, et al. 1995. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. *Life Sci*, 56:2111–8.

Hohmann AG, Suplita RL, Bolton NM, et al. 2005. An endocannabinoid mechanism for stress-induced analgesia. *Nature*, 435:1108–12.

Holdcroft A, Maze M, Dore C, et al. 2006. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology*, 104:1040–6.

Howlett AC, Johnson MR, Melvin LS, et al. 1988. Nonclassical cannabinoid analgetics inhibit adenylate cyclase: development of a cannabinoid receptor model. *Mol Pharmacol*, 33:297–302.

Huestis MA, Henningfield JE, Cone EJ. 1992. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *J Anal Toxicol*, 16:276–82.

Janse AFC, Breekveldt-Postma NS, Erkens JA, et al. 2004. Medicinal gebruik van cannabis.: PHARMO Instituut [Institute for Drug Outcomes Research]. 51 p.

Johnson JR, Potts R. 2005. Cannabis-based medicines in the treatment of cancer pain: a randomised, double-blind, parallel group, placebo controlled, comparative study of the efficacy, safety and tolerability of Sativex and Tetranabinex in patients with cancer-related pain.; 2005 March 8-11; Edinburgh, Scotland.

Jones RT, Benowitz N, Bachman J. 1976. Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci*, 282:221–39.

Joy JE, Watson SJ, Benson JA Jr. 1999. Marijuana and medicine: Assessing the science base. Washington, DC: Institute of Medicine.

Karsak M, Gaffal E, Date R, et al. 2007. Attenuation of allergic contact dermatitis through the endocannabinoid system. *Science*, 316:1494–7.

Karst M, Salim K, Burstein S, et al. 2003. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA*, 290:1757–62.

Katona S, Kaminski E, Sanders H, et al. 2005. Cannabinoid influence on cytokine profile in multiple sclerosis. *Clin Exp Immunol*, 140:580–5.

King LA, Carpentier C, Griffiths P. 2005. Cannabis potency in Europe. Addiction, 100:884–6.

Ko MC, Woods JH. 1999. Local administration of delta9-tetrahydrocannabinol attenuates capsaicin-induced thermal nociception in rhesus monkeys: a peripheral cannabinoid action. *Psychopharmacology (Berl)*, 143:322–6.

Kogan NM. 2005. Cannabinoids and cancer. *Mini Rev Med Chem*, 5:941–52.

Lemberger L, Rubin A, Wolen R, et al. 1982. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. *Cancer Treat Rev*, 9(Suppl B):17–23.

Li J, Daughters RS, Bullis C, et al. 1999. The cannabinoid receptor agonist WIN 55,212-2 mesylate blocks the development of hyperalgesia produced by capsaicin in rats. *Pain*, 81:25–33.

Ligresti A, Moriello AS, Starowicz K, et al. 2006. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther*, 318:1375–87.

Liu J, Li H, Burstein SH, Zurier RB, et al. 2003. Activation and binding of peroxisome proliferator-activated receptor gamma by synthetic cannabinoid ajulemic acid. *Mol Pharmacol*, 63:983–92.

Lorenzetti BB, Souza GE, Sarti SJ, et al. 1991. Myrcene mimics the peripheral analgesic activity of lemongrass tea. *J Ethnopharmacol*, 34:43–8.

Lynch ME, Young J, Clark AJ. 2006. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. *J Pain Symptom Manage*, 32:497–501.

Mackie K. 2006. Cannabinoid receptors as therapeutic targets. *Ann Rev Pharmacol Toxicol*, 46:101–22.

Maida V. 2007. The synthetic cannabinoid nabilone improves pain and symptom management in cancer patietns. *Breast Cancer Res Treat*, 103:121–2.

Malfait AM, Gallily R, Sumariwalla PF, et al. 2000. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA*, 97:9561–6.

Manzanares J, Corchero J, Romero J, et al. 1998. Chronic administration of cannabinoids regulates proenkephalin mRNA levels in selected regions of the rat brain. *Brain Res Mol Brain Res*, 55:126–32.

Martin WJ, Hohmann AG, Walker JM. 1996. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus by a cannabinoid agonist: Correlation between electrophysiological and antinociceptive effects. *J Neurosci*, 16:6601–11.

Massa F, Monory K. 2006. Endocannabinoids and the gastrointestinal tract. *J Endocrinol Invest*, 29(3 Suppl):47–57.

McPartland JM, Russo EB. 2001. Cannabis and cannabis extracts: Greater than the sum of their parts? *Journal of Cannabis Therapeutics*, 1:103–32.

Mechoulam R, Ben-Shabat S, Hanus L, et al. 1995. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol*, 50:83–90.

Mehmedic Z, Martin J, Foster S, et al. Delta-9-THC and other cannabinoids content of confiscated marijuana: potency trends, 1993-2003.; 2005 September 10; Leiden, Netherlands. International Association of Cannabis as Medicine.

Müller-Vahl KR, Schneider U, Kolbe H, et al. 1999. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. *Am J Psychiatry*, 156:495.

Munro S, Thomas KL, Abu-Shaar M. 1993. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*, 365:61–5.

Nadulski T, Pragst F, Weinberg G, et al. 2005a. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. *Ther Drug Monit*, 27:799–810.

Nadulski T, Sporkert F, Schnelle M, et al. 2005b. Simultaneous and sensitive analysis of THC, 11-OH-THC, THC-COOH, CBD, and CBN by GC-MS in plasma after oral application of small doses of THC and cannabis extract. *J Anal Toxicol*, 29:782–9.

Neff GW, O'Brien CB, Reddy KR, et al. 2002. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *Am J Gastroenterol*, 97:2117–9.

Nicholson AN, Turner C, Stone BM, et al. 2004. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol,* 24:305–13.

Nicolodi M, Volpe AR, Sicuteri F. 1998. Fibromyalgia and headache. Failure of serotonergic analgesia and N-methyl-D-aspartate-mediated neuronal plasticity: Their common clues. *Cephalalgia*, 18(Suppl 21):41–4.

Notcutt W, Price M, Chapman G. 1997. Clinical experience with nabilone for chronic pain. *Pharmaceutical Sciences*, 3:551–5.

Notcutt W, Price M, Miller R, et al. 2004. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. *Anaesthesia*, 59:440–52.

Nurmikko TJ, Serpell MG, Hoggart B, et al. 2007. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. In press.

Pacher P, Batkai S, Kunos G. 2006. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev*, 58:389–462.

Pate D. 1994. Chemical ecology of cannabis. *Journal of the International Hemp Association*, 2:32–7.

Pérez J. 2006. Combined cannabinoid therapy via na oromucosal spray. *Drugs Today (Barc)*, 42:495–501.

Pertwee RG. 2005. Cannabidiol as a potential medicine. In: Mechoulam R ed. Cannabinoids as therapeutics. Basel, Switzerland: Birkhäuser Verlag. p 47–65.

Pope HG Jr, Gruber AJ, Hudson JI, et al. 2001. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry*, 58:909–15.

Rahn EJ, Makriyannis A, Hohmann AG. 2007. Activation of cannabinoid CB(1) and CB(2) receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. *Br J Pharmacol*, 1–13.

Rao VS, Menezes AM, Viana GS. 1990. Effect of myrcene on nociception in mice. *J Pharm Pharmacol*, 42:877–8.

Re L, Barocci S, Sonnino S, et al. 2000. Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromuscular junction. *Pharmacol Res*, 42:177–82.

Richardson JD, Aanonsen L, Hargreaves KM. 1997. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. *Eur J Pharmacol*, 319:R3–4.

Richardson JD, Aanonsen L, Hargreaves KM. 1998a. Antihyperalgesic effects of spinal cannabinoids. *Eur J Pharmacol*, 345:145–53.

Richardson JD, Aanonsen L, Hargreaves KM. 1998b. Hypoactivity of the spinal cannabinoid system results in NMDA-dependent hyperalgesia. *J Neurosci*, 18:451–7.

Richardson JD, Kilo S, Hargreaves KM. 1998c. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain*, 75:111–9.

Rog DJ, Nurmiko T, Friede T, et al. 2005. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. *Neurology*, 65:812–19.

Russo E. 1998. Cannabis for migraine treatment: The once and future prescription? An historical and scientific review. *Pain*, 76:3–8.

Russo EB. 2001. Hemp for headache: An in-depth historical and scientific review of cannabis in migraine treatment. *Journal of Cannabis Therapeutics*, 1:21–92.

Russo EB. 2004. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuroendocrinol Lett*, 25:31–9.

Russo EB. 2006a. The role of cannabis and cannabinoids in pain management. In: Cole BE, Boswell M eds. Weiner's Pain Management: A Practical Guide for Clinicians. 7th ed. Boca Raton, FL: CRC Press. p 823–44.

Russo EB. 2006b. The solution to the medicinal cannabis problem. In: Schatman ME, ed. Ethical issues in chronic pain management. Boca Raton, FL: Taylor and Francis. p 165–194.

Russo EB, Guy GW. 2006. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses*, 66:234–46.

Russo EB, Guy GW, Robson PJ. 2007a. Cannabis, pain and sleep: lessons from therapeutic clinical trials of Sativex® cannabis based medicine. *Chem Biodivers*, 4:1729–43.

Russo EB, Mathre ML, Byrne A, et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug Program: An examination of benefits and adverse effects of legal clinical cannabis. *Journal of Cannabis Therapeutics*, 2:3–57.

Samaha AN, Robinson TE. 2005. Why does the rapid delivery of drugs to the brain promote addiction? *Trends Pharmacol Sci*, 26:82–7.

Sarchielli P, Pini LA, Coppola F, et al. 2007. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. *Neuropsychopharmacology*, 32:1384–90.

Schaefer CF, Brackett DJ, Gunn CG, et al. 1979. Decreased platelet aggregation following marihuana smoking in man. *J Okla State Med Assoc*, 72:435–6.

Schley M, Legler A, Skopp G, et al. 2006. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. *Curr Med Res Opin*, 22:1269–76.

Shen M, Piser TM, Seybold VS, et al. 1996. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *J Neurosci*, 16:4322–34.

Smith NT. 2002. A review of the published literature into cannabis withdrawal symptoms in human users. *Addiction*, 97:621–32.

Solowij N, Stephens RS, Roffman RA, et al. 2002. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA*, 287:1123–31.

Spadone C. 1991. Neurophysiologie du cannabis [Neurophysiology of cannabis]. *Encephale*, 17:17–22.

Stott CG, Ayerakwa L, Wright S, et al. 2007. Lack of human cytochrome P450 induction by Sativex. 17th Annual Symposium on the Cannabinoids. Saint-Sauveur, Quebec, Canada: International Cannabinoid Research Society. p 211.

Stott CG, Guy GW, Wright S, et al. 2005a. The effects of cannabis extracts Tetranabinex and Nabidiolex on human cyclo-oxygenase (COX) activity. June 2005; Clearwater, FL. International Cannabinoid Research Society.

Stott CG, Guy GW, Wright S, et al. 2005b. The effects of cannabis extracts Tetranabinex and Nabidiolex on human cytochrome P450-mediated metabolism. June 27 2005; Clearwater, FL. International Cannabinoid Research Association. p 163.

Strangman NM, Walker JM. 1999. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. *J Neurophysiol*, 82:472–7.

Svendsen KB, Jensen TS, Bach FW. 2004. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*, 329:253.

Tambe Y, Tsujiuchi H, Honda G, et al. 1996. Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. *Planta Med*, 62:469–70.

Tashkin DP. 2005. Smoked marijuana as a cause of lung injury. *Monaldi Arch Chest Dis*, 63:93–100.

Topol EJ. 2004. Failing the public health – rofecoxib, Merck, and the FDA. *N Engl J Med*, 351:1707–9.

Volfe Z, Dvilansky A, Nathan I. 1985. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. *Int J Clin Pharmacol Res*, 5:243–6.

Wade DT, Makela P, Robson P, et al. 2004. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler*, 10:434–41.

Wade DT, Makela PM, House H, et al. 2006. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler*, 12:639–45.

Wade DT, Robson P, House H, et al. 2003. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*, 17:18–26.

Walker JM, Hohmann AG, Martin WJ, et al. 1999a. The neurobiology of cannabinoid analgesia. *Life Sci*, 65:665–73.

Walker JM, Huang SM, Strangman NM, et al. 1999b. Pain modulation by the release of the endogenous cannabinoid anandamide. *Proc Nat Acad Sci USA*, 96:12198–203.

Walker JM, Huang SM. 2002. Cannabinoid analgesia. *Pharmacol Ther*, 95:127–35.

Ware M, Wang W, Shapiro S, et al. 2007. Smoked cannabis for chronic neuropathic pain: results of a pilot study. 17th Annual Symposium on the Cannabinoids. Saint-Sauveur, Quebec, Canada: International Cannabinoid Research Society p31.

Wirth PW, Watson ES, ElSohly M, et al. 1980. Anti-inflammatory properties of cannabichromene. *Life Sci*, 26:1991–5.

Wright S. 2005. GWMS001 and GWMS0106: maintenance of blinding. London: GW Pharmaceuticals. 8 p.

Zajicek J, Fox P, Sanders H, et al. 2003. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet*, 362:1517–26.

Zajicek JP, Sanders HP, Wright DE, et al. 2005. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry*, 76:1664–9.

Zuardi AW, Guimaraes FS. 1997. Cannabidiol as an anxiolytic and antipsychotic. In: Mathre ML, editor. Cannabis in medical practice: a legal, historical and pharmacological overview of the therapeutic use of marijuana. Jefferson, NC: McFarland. p 133–41.