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Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report

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Abstract

Introduction: Prescription drug overdoses are the leading cause of accidental death in the United States. Alternatives to opioids for the treatment of pain are necessary to address this issue. Cannabis can be an effective treatment for pain, greatly reduces the chance of dependence, and eliminates the risk of fatal overdose compared to opioid-based medications. Medical cannabis patients report that cannabis is just as effective, if not more, than opioid-based medications for pain.

Materials and Methods: The current study examined the use of cannabis as a substitute for opioid-based pain medication by collecting survey data from 2897 medical cannabis patients.

Discussion: Thirty-four percent of the sample reported using opioid-based pain medication in the past 6 months. Respondents overwhelmingly reported that cannabis provided relief on par with their other medications, but without the unwanted side effects. Ninety-seven percent of the sample "strongly agreed/agreed" that they are able to decrease the amount of opiates they consume when they also use cannabis, and 81% "strongly agreed/agreed" that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids. Results were similar for those using cannabis with nonopioid-based pain medications.

Conclusion: Future research should track clinical outcomes where cannabis is offered as a viable substitute for pain treatment and examine the outcomes of using cannabis as a medication assisted treatment for opioid dependence.

Keywords: opiates; pain; harm reduction; substitution; opioids; cannabis

Introduction

The Centers for Disease Control (CDC) and Prevention report that "[o]pioids (including prescription opioid pain relievers and heroin) killed more than 28,000 people in 2014, more than any year on record." Unfortunately, this statistic has done little to curb the prescribing and consumption patterns for prescription opioids. The CDC estimates that, "since 1999, the amount of prescription opioids sold in the United States nearly quadrupled, yet there has not been an overall change in the amount of pain that Americans report. Deaths from prescription opioids—drugs like oxycodone, hydrocodone, and methadone—have also quadrupled since 1999."[1] Interestingly, Bachhuber et al. found that states with medical cannabis laws had significantly lower state-level opioid overdose mortality rates.[2] Similarly, Bradford and Bradford evaluated data on all prescriptions filled by Medicare Part D patients from 2010 to 2013 and found that the use of prescription drugs for which cannabis could serve as a clinical alternative fell significantly, once a state medical cannabis law was implemented. They found that implementing an effective medical cannabis law led to a reduction of 1826 daily doses for opioid pain relief filled per physician per year.[3]

Patients who suffer with pain continue to use opioids for chronic pain conditions despite their limited long-

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term efficacy. The management of chronic pain impacts 11.2% of adults in the United States with about 3% to 4% of these patients receiving long-term opioid therapy.[4] This translates to ~100 million Americans and incurs costs of up to $635 billion dollars per year.[5] Long-term opioid therapy is associated with a number of risks, including opioid use disorder, overdose, and death. In 2012 the National Institute of Drug Abuse estimated that there were ~2.1 million people in the United States suffering from substance use disorders related to prescription opioid pain relievers and another half million addicted to heroin.[6]

Used in combination with opioid pain medications, cannabis can lower opioid side effects, cravings, and withdrawal severity, as well as enhance the analgesic effects of opioids, thereby allowing for lower doses and less risk of overdose.[7,8] A previous study reported that their subjects' pain "was significantly decreased after the addition of vaporized cannabis" and suggested that cannabis treatment "may allow for opioid treatment at lower doses with fewer [patient] side effects." The authors concluded that their results "demonstrate that inhaled cannabis safely augments the analgesic effects of opioids."[9] Research published last year found that 80% of medical cannabis users reported substituting cannabis for prescribed medications, particularly among patients with pain-related conditions.[8]

In an 1889 seminal article published in *The Lancet*, Dr. Edward A. Birch writes about his tremendous success in using cannabis to help patients who had become addicted to pain medications, including opioids. He wrote, "I prescribed the cannabis simply with a view to utilizing a well-known remedy for insomnia, but it did much more than procure sleep. I think it will be found that there need be no fear of peremptorily withdrawing the deleterious drug, if hemp be employed." (p. 625).[10] Birch's comments from 127 years ago predicted what we know to be true today, despite some controversy that continues to surround the topic of cannabis as medicine. Numerous scholarly studies have demonstrated the efficacy of cannabis for multiple conditions, including the management of pain, while concurrently reducing the reliance on opioid medications and nonopioid medications.[5] In a 2010 pain study conducted in Canada, Ware et al. found that "a single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep, and was well tolerated."[11]

While the use of cannabis to treat pain is becoming more accepted in the United States, the Schedule I status of cannabis has made it difficult to conduct large-scale clinical trials on its efficacy. Recent clinical and systematic reviews have acknowledged the promise that cannabis might hold as a standardized pain treatment, while recognizing the limitations that come from small sample sizes and lack on controlled studies. While these reviews show moderate evidence for cannabis as a treatment for pain-related conditions, they also call for additional research in the form of standardized clinical trials.[12,13] Meanwhile, in parallel, medical cannabis patients are reporting the use of cannabis to treat their pain in lieu of or in conjunction with opioid-based pain medications.

The act of substituting cannabis for opioids has also been documented in several studies of medical cannabis patients. Consistently, these studies saw substitution rates for prescription drugs over 50%, with less side effects from cannabis being a top reason for substitution across studies.[14–16] Given the efficacy data on how cannabis assists patients' management of pain, while also mitigating the risks associated with long-term opioid therapy, the present study uses data gathered directly from the impressions of patients who have used cannabis. Patients were provided an opportunity to comment on how cannabis compared with their use of opioid and nonopioid-based pain medication for the treatment of pain.

Materials and Methods

This study utilized a cross-sectional survey to gather data about the use of cannabis as a substitute for opioid and nonopioid-based pain medication. This study was approved by the IRB at the University of California, Berkeley (Protocol No. 2016-08-9044). Drs. Welty and Reiman did not receive compensation from HelloMD to complete the study.

Instrument

The survey instrument (see Supplementary Appendix SA1 for a copy of the instrument) used for this study was a modified version of the survey used in the Tilray Observational Patient Survey (TOPS). The survey for this study included questions about demographic characteristics, conditions for which cannabis is used, and preferred method of cannabis ingestion. Participants were then asked about their use of cannabis as a substitute for opioid and nonopioid-based pain medication to create subsets of respondents who were engaging in substitution. An affirmative answer led participants to the sections that asked about their experiences using cannabis as a substitute. Questions in this section asked about perceived efficacy of cannabis compared to their other medications,

perceived comparability of unwanted side effects, and how the stigma around cannabis impacts their decision to use it as a substitute.

Sampling

The survey was administered through e-mail to a database of 67,422 medical cannabis patients in the state of California using the HelloMD patient database. HelloMD is a digital cannabis health and wellness platform that also provides Telehealth evaluations for medical cannabis recommendations to patients in California. The members of the database received an invitation e-mail describing the study and the survey, along with a link to the survey. After clicking the link, respondents were taken to the Qualtrics survey site where they could complete the survey confidentially. A reminder e-mail with the link to the survey was sent out 2 weeks after the initial invitation was sent. The survey was closed 4 weeks after the reminder e-mail was sent. As an incentive for participating, upon completion of the survey, respondents were asked if they would like to enter a raffle for one of five Firefly vaporizers. If they wished to enter, they clicked on a link that directed them to a form where they could enter their name and e-mail address. At the completion of the sampling, five respondents were selected at random and awarded the vaporizer.

Results

Demographics

Of the 2897 participants, 55% were male. Eleven respondents identified as trans males and one identified as a trans female. Fifty-three percent of the sample was between the ages of 20 and 39, 29% being over the age of 50, and 15% over the age of 60. Sixty-four percent identified as White, 14% Latino(a), and 7% African American. Most patients had some college education or completed college (71%) with 14% having completed postgraduate work. There were some significant differences between the general sample and those reporting past 6 month use of opioid and nonopioid-based pain medications. Whites were significantly more likely to report past 6 month use of both types of pain medication ($p < 0.001$). Age was also significantly related to past 6 month use of these medications ($p < 0.001$). Other significant determinants were being a woman ($p < 0.001$) and having a pain condition ($p < 0.001$) (Table 1).

Table 1. Sample Demographics

	N (%)
Male	1593 (55)
20–29	898 (31)
30–39	666 (23)
40–49	406 (14)
50–59	406 (14)
60+	435 (15)
White (not Hispanic)	1854 (64)
Hispanic/Latino(a)	406 (14)
African American	203 (7)
Asian	145 (5)
Pacific Islander	29 (1)
American Indian	58 (2)
Other ethnicity	203 (7)
High school	435 (15)
Some college	1130 (39)
College graduate	927 (32)
Graduate school	406 (14)

Condition and cannabis use

Pain was the most common condition for which respondents reported using cannabis with 16% reporting that as their primary condition. However, when accounting for all pain-related conditions (menstrual cramps, fibromyalgia, back pain and arthritis, etc.) that rises to 63%. Common mental health conditions for which respondents used cannabis included anxiety (13%), insomnia (9%), and depression (5%) (Fig. 1). Smoking was the most common method of ingestion with 50% of the sample reporting using cannabis in that way. Thirty-one percent report vaporizing their cannabis, and 10% use edibles. Three percent reported that they do not currently use medical cannabis.

Cannabis and opioids

Thirty percent of the sample ($N = 841$) reported using an opioid-based pain medication currently or in the past 6 months. Of those who have used opioids, 61% reported using them with cannabis. Ninety-seven percent of the sample "strongly agreed/agreed" that they are able to decrease the amount of opioids they consume when they also use cannabis. In addition, 89% "strongly agreed/agreed" that taking opioids produces unwanted side effects such as constipation and nausea. Ninety-two percent of the sample "strongly agreed/agreed" that cannabis has more tolerable side effects than the opioid-based medications they have taken. Eighty-one percent "strongly agreed/agreed" that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids. When asked if cannabis produces the same amount of pain relief as their opioid-based medications, 71% "strongly agreed/agreed" with that fact. Ninety-two percent of the sample "strongly agreed/agreed" that they prefer cannabis to opioids for the treatment of their condition and 93% "strongly agreed/agreed" that they would be

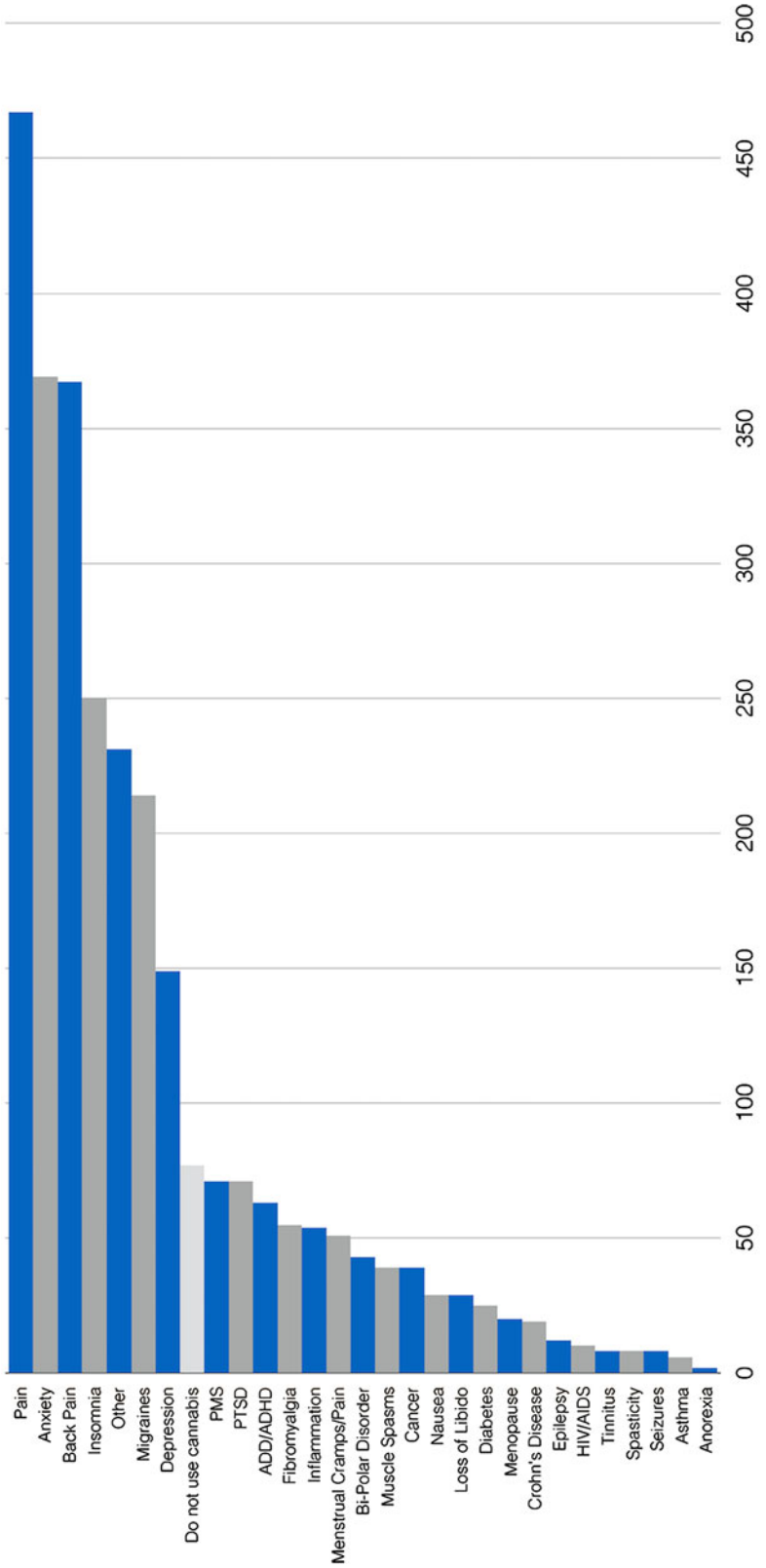

FIG. 1. Primary conditions.

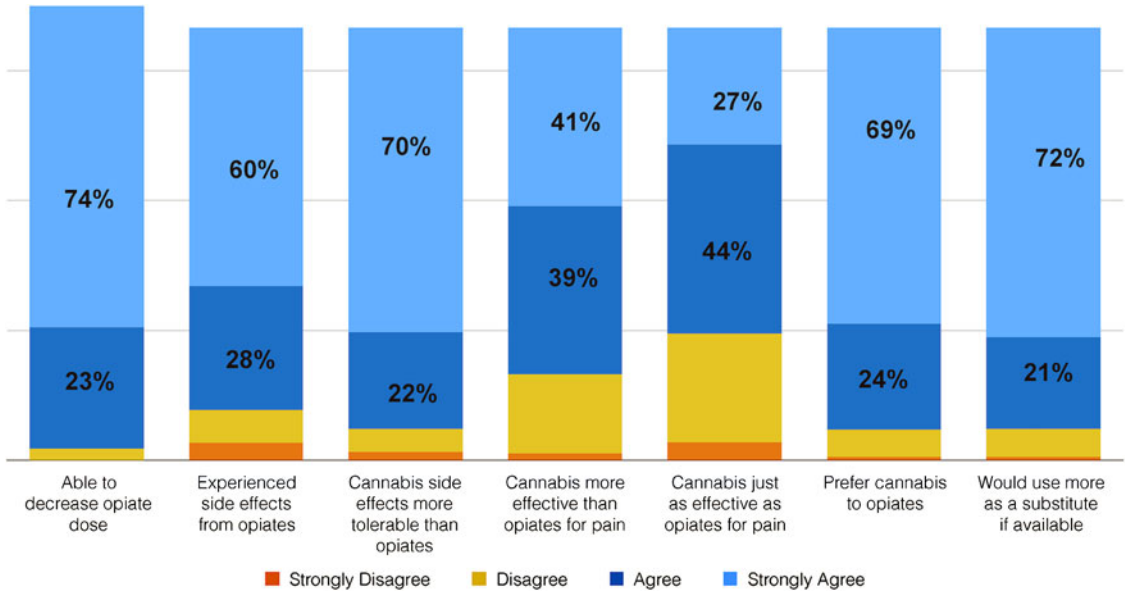

FIG. 2. Use of cannabis as a substitute/in conjunction with opioid-based pain medication ($n = 828$).

more likely to choose cannabis to treat their condition if it were more readily available (Fig. 2).

Cannabis and nonopioid-based medications

Sixty-four percent of the sample ($N = 1751$) reported taking a nonopioid-based pain medication (e.g., Tylenol) for their condition currently or in the past 6 months. Seventy-six percent of the sample reported taking a nonopioid-based pain medication along with cannabis currently or in the past 6 months. Ninety-six percent "strongly agreed/agreed" that they do not need to take as much of their nonopioid-based pain medication when they use cannabis and 92% "strongly agreed/agreed" that cannabis works better for their condition than a nonopioid-based pain medication.

As for preferring cannabis over nonopioid pain medication, 95% "strongly agreed/agreed" with this statement.

Similarly to the opioid pain medication group, 93% reported that they would be more likely to use cannabis as a substitute if it were more readily available and easier to access (Fig. 3).

Discussion

Supporting the results of previous research, this study can conclude that medical cannabis patients report successfully using cannabis along with or as a substitute for opioid-based pain medication. Echoing the results of Ware et al. and Abrams et al., patients in this study who are using cannabis and opioids report that they are able to use less opioids and that cannabis presents less unwanted side effects than their opioid-based medication.[9,11] In addition, 80% of patients reported that cannabis by itself was more effective than their opioids. It is possible that the variability of individual endocannabinoid and endo-opioid systems results in varying levels of efficacy between the two treatments. For example, a recent review released by the National Academy of Sciences reports conclusive evidence cannabis' efficacy in treating chronic pain, but localized versus neuropathic pain might demand different approaches.[17] Cannabis has been found to be very useful in treating neuropathic pain specifically.[11]

This study found a similar pattern of results when looking at substituting cannabis for nonopioid-based pain medication like Tylenol and Advil. Research suggests that long-term use of these remedies might lead to organ damage.[18] With cannabis not only becoming more accepted in the mainstream but also coming in a variety of preparations, some of which are nonintoxicating, more people are looking at cannabis as a viable treatment for everyday ailments such as muscle soreness and inflammation. The

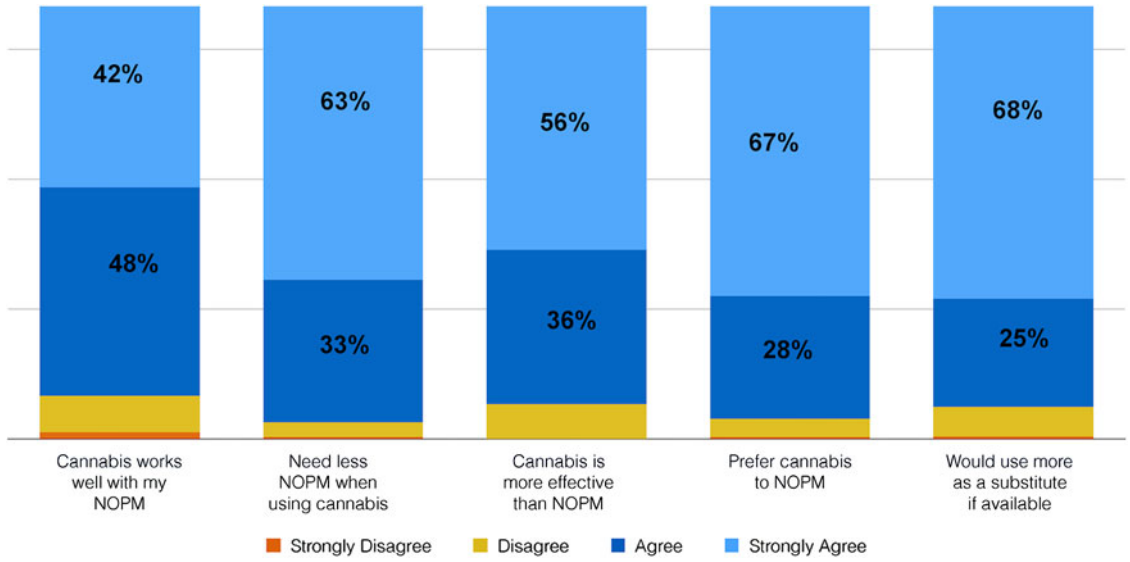

FIG. 3. Use of cannabis as a substitute/in conjunction with nonopioid based medication ($n = 1684$).

results of this study support that not only is this practice common but also medical cannabis patients who choose to use cannabis as a substitute for these medicines report better outcomes with fewer unwanted side effects with cannabis compared to their other medications.

Participants in this study overwhelmingly supported the notion that they would be more likely to use cannabis as a substitute for pain medication if it were less stigmatized and more available, suggesting that there are populations of people who could benefit from this practice but are shying away due to the stigma and legal restrictions related to cannabis use. If cannabis laws continue to change across the country, it will be important to assess how changes in these laws might impact other public health behaviors and outcomes, such as opioid overdose, dependence, risky behaviors, and spending on prescription medications.

Limitations

This is a study of patient self-report through online survey. The data for analyses are based on patient perception and not on objective measure of cannabis and opioid use. Furthermore, there is no comparison group of pain patients who only have access to opioid-based medications or individuals solely using over-the-counter medications for pain. Finally, the solicitation e-mail sent to potential participants included the title of the study which relates to cannabis use for pain. This may have biased the respondents toward those using for pain versus other conditions.

Response rate

The survey yielded responses from 2897 participants, which is a response rate of 4.3%. Since the survey was sent to the HelloMD total patient database, including those not using cannabis for pain, this could reflect in the response rate. Other reasons for nonresponse, besides lack of interest, include people who are no longer patients and those who chose not to participate for other reasons such as privacy concerns.

Amount of cannabis consumed

One of the major limitations of cannabis research is the difficulty in determining how much cannabis participants are using. Variations in strength of product, size of vessel, and social use patterns all impact the reliability and validity of consumption measures. This survey did not ask participants to estimate their amount of consumption and therefore cannot comment on reported effective doses.

Prescription status of opioids

This study did not ask participants if the opioids they consumed were from a prescription or by self-medication. The study also did not inquire as to the specific types of opioids being consumed.

Conclusions

The results of this study provide implications from both a micro and macro level. First, from the macro level, there have been three previously published indicators of public health changes in states that permit medical cannabis: decreases in opioid related mortality, decreases in spending on opioids, and a decrease in traffic fatalities.[2,3,19] While none of these studies shows a cause and effect relationship, they do suggest public health related population based changes in localities where cannabis can be accessed to treat pain. Given that the participants in this study reported a greater likelihood of using cannabis as a substitute in a less stigmatized and easily accessible environment, it makes sense why we would see these changes in locations where medical cannabis is sanctioned versus places where it is illegal.

At the micro level, there is a great deal of individual risk associated with prolonged use of opioids and perhaps even nonopioid-based pain medications. The prescribing of opioids has not been curbed in the United States, despite the growing number of fatal overdoses and reported dependence. Providing the patient with the option of cannabis as a method of pain treatment alongside the option of opioids might assist with pain relief in a safer environment with less risk. A society with less opioid dependent people will result in fewer public health harms.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

CDC = Centers for Disease Control
TOPS = Tilray Observational Patient Survey

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Review Article

Clinical uses of cannabis and cannabinoids in the United States

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ABSTRACT

The role of cannabis in medicine is rapidly evolving. Medical cannabis is now legal in a majority of states, and THC and CBD, the prominent cannabinoids found in cannabis, have both been utilized in the development of FDA-approved drugs. Due to the complicated legal status of cannabis and cannabinoids, as well as regulations that vary from state to state, the appropriate use of these substances for both patients as well as clinicians is often unclear. Advancements in the understanding of the pharmacology of cannabis have led to numerous proposed uses of these drugs, including as antidepressant or analgesic agents. However, clinical trial data for these substances suggests that many purported indications of cannabis and cannabinoids are not supported by good clinical data. Furthermore, cannabis and several cannabinoid-based medications have potentially concerning side effect profiles that may limit their use in certain patient populations. As the legal status and clinical database of these medications continue to evolve, physicians will need to continue to balance the real potential of these compounds with their limitations and adverse effects.

1. Introduction

Though the role of cannabis in society has evolved over several millennia, it may be going through its most rapid period of change to date. In 1996, California became the first state to legalize the use of cannabis with the approval of a physician, known widely as “medical marijuana.” As of January 2020, 33 states and the District of Columbia have legalized the use of cannabis for medical purposes, and 12 states and DC have gone a step further to legalize the recreational use of cannabis [1].

In addition to the sociocultural, legal, and economic impacts of these legislative changes, the widespread expansion of cannabis and cannabis-related products has had a marked impact on the medical field. Recently, cannabis has been perceived as being safer and use of the drug has increased [2]. Approximately 10% of cannabis users in the United States use the drug to treat a medical condition [3]. Cannabis now occupies a unique position as both a schedule I narcotic (indicating that there are no acknowledged medical uses of the drug), as well as a substance with various purported health benefits (such as antidepressant, hypnotic, and analgesic effects) that clinicians may indirectly offer to patients through certification.

Further complicating the picture, the Food and Drug Administration (FDA) has approved three medications based on compounds contained in cannabis for various indications [4]. Additionally, CBD (cannabidiol; a cannabinoid found in cannabis) is now widely available in non-medical settings, such as coffee shops and tobacco stores, in several US states. CBD has been advertised to treat a wide array of medical conditions, and sales of CBD-related products continue to grow rapidly [5].

These rapid changes are not unique to the United States. The majority of European Union member-states have authorized the use of cannabis-derived medications [6]. However, laws can vary widely between nations with respect to legal status and insurance coverage [7,8]. Furthermore, even within countries there can be gaps between the legal status of a drug and its actual availability to patients [6].

These developments present a unique challenge to physicians. Clinicians now face the dual task of avoiding harms related to the most widely-abused drug in the United States [2], as well as identifying appropriate and evidenced-based indications for the use of cannabis or cannabis-related products. This is further complicated by patients often receiving misinformation from parties with vested interests in the debate over these substances. State-level regulations provide little clarity as there are over 50 medical conditions that various states list as appropriate indications for cannabis despite little evidence to support such prescribing practices [9].

This review will attempt to clarify the science behind the use of cannabis and cannabis-related drugs, and provide guidance for the clinician attempting to safely balance the risks and benefits that these drugs carry.

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This manuscript primarily focuses on recent developments in the appropriate use of cannabis and cannabinoid-based medications. Relevant studies were identified by reviewing the available medical literature in PubMed for between 1948 and October 2019 pertaining to the medical use of cannabis and cannabinoids, with a focus on meta-analyses and randomized clinical trials.

2. Pharmacology

Cannabis comes from the *Cannabis sativa* plant and contains over 140 pharmacologically-active cannabinoids [10]. The two most prominently-studied cannabinoids, as well as the two thought to be most pharmacologically-relevant compounds are delta-9-tetrahydrocannabinol (THC) and CBD. THC and CBD share several pharmacologic properties, such as poor bioavailability and high lipophilicity [11]. However, the receptor profile of these compounds differs markedly, and their divergent physiologic effects are explained in large part by their interaction (or lack thereof) with the endocannabinoid system.

Endocannabinoid receptors are G-protein-coupled receptors that interact with endogenous cannabinoids (*endocannabinoids*) [12]. These receptors, named CB1 and CB2, are differentially found primarily in the basal ganglia, hippocampus, cerebellum, cerebral cortex, and peripheral nervous system (CB1), or on cells in the immune system (CB2) [13]. These receptors have effects on multiple downstream neurotransmitters including serotonin, acetylcholine, dopamine, glutamate, and GABA, as well as NMDA and opioid receptor systems [14].

THC is a partial agonist at both CB1 and CB2 receptors [15]. THC is thought to be predominantly responsible for the psychotropic effects of cannabis, and agonism at the CB1 receptor is the likely mechanism for its pro-psychotic and euphoric effects [15]. In addition to psychiatric properties, some evidence suggests that THC may also have analgesic and anti-inflammatory properties [12]. Notably, the concentration of THC in *Cannabis sativa* has been increasing over time (4% in 1995 to 12% in 2014) [16].

In contrast, CBD is a CB1 antagonist and CB2 negative allosteric modulator, and generally has a low level of activity at these receptors compared to THC [17]. The contrary receptor profiles of THC and CBD have been found to correspond to opposing functional MRI blood oxygenation signatures in several basal ganglia and cortical areas during cognitive tasks [18]. This same study also found that pretreatment with CBD ameliorated THC-induced psychotic symptoms, further suggesting that the THC-based agonism of CB1 is counteracted by the negative allosteric of CBD at this receptor.

In addition to cannabinoid receptor-dependent properties (such as possible anti-inflammatory effects from CB2 negative allosteric modulation), CBD has many cannabinoid receptor-independent properties. CBD is also a capsaicin analog and agonist at the TRPV1 receptor [17]. Furthermore, CBD has agonist properties at the 5HT1A receptor, which are thought to perhaps facilitate the anxiolytic properties of CBD [19]. Lastly, CBD has physiologic properties that are not yet clearly related to a specific mechanism, such as antioxidant, anticonvulsant, analgesic, and immunomodulatory functions [20].

Given that CBD and THC, the predominant cannabinoids found in cannabis, display distinct and often opposite physiologic properties, it should not be surprising that the two have very different therapeutic indications and adverse effect profiles (Table 1). For this reason, cannabis and medications containing THC are discussed separately from medications containing only CBD.

3. Cannabis and THC analogs

3.1. Indications

Estimates suggest that over two million Americans utilize cannabis for medical purposes [30]. There are many proposed medical uses of cannabis; internationally, the most uses include post-injury pain, depression, sleep disorders, multiple sclerosis (MS), and back pain [15]. This represents only a small fraction of suggested medical benefits of cannabis. Several of these indications are supported by good scientific evidence, but many are not.

Despite its medicalization and legalization, cannabis remains a schedule I narcotic. Medical cannabis is, therefore, not prescribed by physicians, but rather obtained at dispensaries after a physician has licensed its use for a given indication. Notably, medical cannabis is not a “special” or even standardized form of cannabis, meaning that the THC and CBD content of cannabis obtained for a medical indication is completely unstandardized [13]. In other words, medical cannabis and recreational cannabis are not meaningfully distinct terms from a pharmacologic perspective.

State rules on medical cannabis vary widely and include indications with high-quality as well as low-quality evidence. Indications range from post-traumatic stress disorder to hepatitis C, and states also differ on the quantity of cannabis that patients may have at a given time [13]. The best evidence exists for the role of cannabis in alleviating pain and spasticity due to MS. A 2018 meta-analysis examined 17 randomized clinical trials (RCTs) of both cannabis in standardized dosages and relative THC:CBD ratios as well as cannabinoid-based medications for this use [31]. Totaling over 3000 patients, aggregate data showed modest, though statistically significant, positive effects on pain, spasticity, and bladder dysfunction. In 2014, the American Academy of Neurology published a set of specialty guidelines that identified nabiximols, a combination THC-CBD medication, as having the highest level of empirical evidence for the treatment of pain and spasticity associated with MS [26]. Notably, nabiximols (trade name Sativex®) is available in many European countries for the treatment of neuropathic pain due to MS, though is not approved in the US [32].

In addition to medical cannabis, there are two FDA medications that act as THC analogs. Nabilone (trade name Cesamet®; [23]) and dronabinol (trade name Syndros® or Marinol®; [22]) have both received FDA approval for chemotherapy-induced nausea and vomiting, as well as cachexia related to HIV or cancer. Though neither medication is typically believed to be a first line option, society guidelines now identify these agents as reasonable for symptoms refractory to first-line agents [21].

Beyond these indications, the evidence for the use of cannabis or THC-based cannabinoids ranges from equivocal to very weak [13]. One oft-cited indication is chronic pain. Theoretically, given that endocannabinoids modulate pain and CB1 receptors are present in nociceptors on peripheral nerves, cannabis appears to be promising analgesic [33]. However, a 2017 meta-analysis of 27 studies examining the effectiveness of cannabis in treating chronic pain found only weak evidence that cannabis alleviates neuropathic pain, and no evidence suggesting that cannabis was useful in other types of pain [34]. Another meta-analysis specifically examining the use of cannabis to treat non-cancer related chronic pain found that the number needed to treat to achieve a 50% reduction in pain was 24, whereas the number needed to harm for any adverse effect of cannabis was only 6, suggesting that the benefits of cannabis use were outweighed by possible harms [35]. One theory posits that the therapeutic window for the analgesic properties of cannabis is relatively narrow [33]. It should be noted, however, that some professional organizations have been more receptive to the use of cannabis as an analgesic—in their 2017 report on cannabis, the National Academies of Sciences, Engineering, and Medicine found a clinically significant (albeit modest) effect of cannabis and cannabinoids on chronic pain [[28]].

Many states identify glaucoma as an approved condition for medical cannabis [13]. However, while there is some evidence for cannabis use leading to a decrease in intraocular pressure, this effect is quite ephemeral, lasting only three to 4 h [36]. The American Academy of Ophthalmology released a position statement in 2014 stating that the risks associated with chronic use of cannabis outweighed the benefits, and thus they did not recommend the use of cannabis for glaucoma

Table 1
Summary of the pharmacologic, legal, and clinical differences between THC and CBD.

	THC	CBD
Receptor profile and notable physiologic properties	Partial agonist at CB1 and CB2 receptors. Noted to have anti-inflammatory, analgesic, psychotomimetic, and euphoric properties.	CB1 antagonist, CB2 negative allosteric modulator, capsaicin analog, TRPV1 agonist. 5HT1A agonist. Noted to have anti-inflammatory, immunomodulatory, antioxidant, anticonvulsant, analgesic effects.
Legal status in the United States	THC (and thus cannabis) is still considered a schedule I substance in that it has no officially recognized medical use. Specific laws vary from state to state with respect to medical or recreational usage.	CBD without THC is available without a license or prescription and can easily be obtained at grocery stores, restaurants, and other non-medical businesses.
Pharmaceuticals based on active ingredient and FDA indication	Nabilone (Cesamet®) and dronabinol (Syndros®, Marinol®); chemotherapy-induced nausea and vomiting [21–23], cachexia related to HIV or cancer [22].	Epidiolex®; seizures associated with Dravet or Lennox-Gastaut syndromes [24,25].
Investigational uses supported by high-quality clinical evidence	Pain and spasticity related to MS [26,27], possibly other forms of chronic pain [28].	Other types of treatment-resistant epilepsy [29].
Notable adverse effects associated with use	Acutely, tachycardia, euphoria, impaired judgment and concentration, psychosis. Chronically, chronic bronchitis (if smoked), risk of abuse and dependence, possibly an increased risk of developing a chronic psychotic or depressive disorder, lower IQ.	Acutely, somnolence, diarrhea, fatigue, and anorexia. May inhibit CYP450 isozymes. No known chronic adverse effects. Generally well-tolerated.

5HT1A, serotonin 1A receptor; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; CBD, cannabidiol; CYP450, cytochrome P450; HIV, human immunodeficiency virus; IQ, intelligence quotient; MS, multiple sclerosis; THC, delta-9-tetrahydrocannabinol; TRPV1, transient receptor potential cation channel subfamily V member 1.

[36].

A comprehensive 2015 systematic review and meta-analysis that examined 79 RCTs and a total of 6462 for a variety of physical and mental health conditions well demonstrates many of the challenges of making clear recommendations for the medical use of cannabis and cannabinoids [27]. Notably, only 4 of these RCTs were judged as having a low risk of bias. Many of the included RCTs suffered from small sample size, inadequate randomization and blinding, and other methodological issues. The small sample sizes are particularly challenging as the use of cannabis in treating several indications (such as pain and spasticity) showed some possible benefit that did not reach statistical significance. Furthermore, heterogeneity in specific pharmacologic agent, dose, and route of administration complicates straightforward comparison and data aggregation. Ultimately, the study found moderate-quality evidence of cannabinoids for neuropathic and cancer pain as well as spasticity in MS, and low-quality evidence for other conditions (including nausea and vomiting due to chemotherapy, sleep disorders, and several mental health conditions).

Similarly, a 2019 systematic review and meta-analysis specifically sought to evaluate the evidence for cannabis and cannabinoids in treating mental health conditions such as depression, anxiety, post-traumatic stress disorder (PTSD), psychosis, and attention-deficit hyperactivity disorder (ADHD) [37]. This study also noted a lack of high-quality randomized clinical trials, small sample sizes, and the difficulty of standardizing across studies. The meta-analysis found only very low-quality evidence for the use of cannabinoids in treating anxiety disorders in patients with other medical conditions, and no evidence for the other indications studied. The authors succinctly summarized their findings in concluding their study: “In light of the paucity of evidence and absence of good quality evidence, and the known risk of cannabinoids, the use of cannabinoids as treatments for mental disorders cannot be justified at this time” [37].

The largely negative results seen in trials of using cannabis to treat a variety of conditions likely reflects a number of challenges in adapting cannabis for medical usage. First, as mentioned previously, medical cannabis is simply recreational cannabis that has been licensed by a physician for a given use. This means that two patients using medical cannabis may be utilizing very different drugs depending on the THC and CBD content of their two marijuana strains [39]. Although advertisers have attempted to capitalize by marketing certain strains as being specially formulated for different causes, this approach is not backed by hard science [13]. Furthermore, dosing is also complicated by the inexactitudes of prescribing a given amount of cannabis. If, for example, cannabis does have a narrow therapeutic range as an analgesic, clinicians may be at a loss as to pick the appropriate dose not knowing how this corresponds to a quantity of the active cannabinoid of interest.

All the above raises the question of how a clinician can responsibly assess a patient for medical cannabis [13]. Clinicians should use a standardized approach to identify patients that are more likely than not to benefit from such treatment and unlikely to experience serious adverse effects. First, such patients should be identified as having a condition where there is high-quality evidence that cannabis or cannabis-based medications have been found to be useful. Additionally, the treatment history should be investigated to see if patients have first undergone adequate trials of FDA-approved medications for these conditions. Clinicians should complete a thorough medical and psychiatric evaluation to identify risk factors that may place patients at greater risk of adverse effects (such as psychotic or substance use disorders; see ‘Adverse Effects’ below). If after an interview and history the physician determines that a patient may benefit from cannabis, they should then discuss the scientific evidence that does or does not support the usefulness of these substances. Beyond medical decision-making, physicians should also discuss legal and logistical concerns with using cannabis, including that it is not available at pharmacies (needs to be obtained at dispensaries), and is rarely covered by insurance (though FDA-approved cannabinoids often are). Lastly, patients who use medical cannabis can also face challenges when they are hospitalized. While rules vary by state and across different healthcare systems, many forbid the use of cannabis while inside hospitals [39]. After collectively deciding to initiate treatment with cannabis or a cannabinoid, close follow-up is strongly recommended.

3.2. Adverse effects

Cannabis use is increasingly seen as being relatively harmless [2]. Cannabis and cannabinoid medications containing THC are discussed together here as the adverse effects of cannabis are similar to those of THC alone, and THC is thought to be responsible for the majority of the adverse effects of cannabis [15]. Notably, the effects of cannabis are not limited to the individual directly smoking the drug—second-hand cannabis smoke can produce effects even with second-hand ingestion [40].

Short-term effects of cannabis use include tachycardia, hypotension, xerostomia, xerophthalmia, euphoria, as well as impaired attention, coordination, and judgment [12,15,41]. Notably, respiratory depression, a major overdose concern with the use of opioids or benzodiazepines, is not an effect of cannabis use as CB1 receptors are not located in the midbrain [12]. Furthermore, there is virtually no risk of lethal overdose with cannabis, as even regular heavy users of cannabis use consume doses of THC that are orders of magnitude smaller than the

theorized lethal dose of approximately 4 g for a 70 kg human [15]. However, cannabis may indirectly have acute lethal effects, as it has been found to double the risk of motor vehicle accidents [42]. At higher doses, cannabis use may also result in psychosis and paranoia [41].

At lower doses the acute side effects of cannabis use may be relatively mild, but chronic adverse effects can be more pronounced. These adverse effects may be conceptually broken into neuropsychiatric and systemic side effects.

Chronic cannabis usage puts patients at risk of multiple neuropsychiatric conditions. Cannabis use has been associated with both depression and anxiety [43]. It has long been known that cannabis use can not only lead to a brief psychotic episode, but may also increase the risk of developing schizophrenia. Current estimates suggest that the risk of schizophrenia in chronic cannabis users is approximately double that of the rest of the population, though the causality of the relationship between cannabis use and the development of psychotic disorders remains controversial [15,44].

Cannabis exposure can be especially detrimental to brains still undergoing development. Prenatal and adolescent exposure to THC can lead to impaired neural connectivity [45]. Some of this impaired neural connectivity has been found to occur in the hippocampus, potentially explaining an association between adolescent cannabis use and decreased IQ [41]. Some preclinical research has suggested, however, that detrimental developmental effects from cannabis smoking may instead be related to non-cannabinoid contaminants [46].

Cannabis is an abusable substance. Given evidence of physiologic dependence and tolerance, as well as documented withdrawal syndromes (occurring in up to 1/3 of chronic users), the 5th Edition of the Diagnostic and Statistical Manual recognizes the diagnosis of cannabis use disorder (CUD) [47]. Among users of cannabis, estimates are that approximately 10% meet criteria for CUD [15]. Concerningly, cannabis abuse is a predictor for future abuse of illicit drugs [41]. As with other consequences of cannabis use, risks associated with CUD are most pronounced in adolescent patients. This may be because in adolescence the endocannabinoid and mesolimbic reward systems, which are affected by cannabis use, continue to actively development until approximately age 21 [41,48,49].

Finally, multiple organ systems outside the central nervous system can be affected by chronic cannabis use. Chronic smokers of cannabis are at increased risk for developing chronic bronchitis, cannabis use mildly increases the risk of myocardial infarction, and there is a moderately increased risk of testicular cancer [15].

4. CBD

4.1. Indications

Preliminary studies of CBD have identified several therapeutically useful properties of the chemical, including anti-inflammatory, antioxidant, antiapoptotic, neuroprotective, analgesic, oncolytic, and immunomodulatory effects [17]. Despite this, there is only one currently FDA-approved CBD-based product, Epidiolex® [50]. Epidiolex® has been approved by the FDA to treat two rare conditions: drug-resistant seizures due to either Dravet syndrome or Lennox-Gastaut syndrome (LGS), or as an add-on therapy for LGS [24,25,51].

Beyond these, CBD has no current FDA-approved uses, though both preclinical and clinical evidence point to possible future uses of the drug. One area of intense interest is the use of CBD to treat psychosis. Preclinical data supports the possible use of CBD to counteract psychogenic properties of THC [18]. Additionally, a 2018 neuroimaging study examining patients at high risk of psychosis showed that CBD normalized fMRI signatures in regions associated with psychosis [52]. Other preclinical work has suggested several mechanisms through which CBD may exert anti-psychotic properties, including antagonism of CB1 receptors, modulation of dopamine signaling, and decreasing neuroinflammation [53,54]. Follow-up RCTs examining the effectiveness of CBD in psychotic disorders has shown mixed results [54]. A 2012 double-blind RCT reported that CBD was as effective as amisulpride, an antipsychotic commonly used to treat schizophrenia, in treating both positive and negative symptoms of schizophrenia and had fewer associated side effects, including extrapyramidal symptoms, hyperprolactinemia, and weight gain [55]. Another RCT comparing CBD with placebo showed a significant improvement in positive symptoms without any difference in adverse effect reporting compared to placebo [56]. However, a 2018 RCT comparing CBD to placebo did not show any significant change in positive or cognitive symptoms [57]. A review of available studies suggests that the opposing effects seen in these studies could be related to dosing of CBD (timing and quantity) as well as the stage of schizophrenia being studied [54]. Therefore, while preliminary evidence has suggested a possible role for CBD as an antipsychotic, the specifics of how—and in whom—the drug should be used are still unclear.

CBD has been tested in mental illness other than schizophrenia as well. It has been found to decrease reported anxiety in patients with social phobia when subjects were exposed to a simulated public speaking exercise [58]. Another study examining patients with social anxiety disorder found that CBD ameliorated symptoms of anxiety and these symptomatic changes corresponded to altered cerebral blood flow on SPECT imaging in anxiety-associated limbic and paralimbic areas [59]. Lastly, some case reports have found that CBD may be useful in treating cannabis withdrawal, though evidence for using CBD for CUD itself is mixed [54].

Beyond utilizing CBD for psychiatric conditions, researchers have also attempted to leverage the neuroprotective effects of CBD in neurodegenerative diseases. In Alzheimer's Disease, promising results have been found in preclinical studies showing CBD promoting neuronal survival and decreasing neuroinflammation, though clinical evidence is lacking at this time [17]. For Parkinson's Disease (PD), clinical studies thus far have shown that CBD may be useful for improving overall well-being and treatment of comorbid psychiatric symptoms [17]. One study of PD patients taking CBD in addition to dopamine-replacement therapy showed a decreased in psychotic symptoms as well as overall decreased in psychiatric symptomatology [60]. Treatment of PD patients with CBD has also been found to reduce the frequency of aggressive behaviors [61]. Notably, however, a double-blind study investigating the effect of CBD on motor symptom severity in PD patients did not show any effect [62]. Similarly, a randomized crossover of patients with Huntington Disease did not show any benefit of CBD in reducing chorea severity [63].

The broad set of potentially beneficial properties of CBD have also led researchers to examine its effects outside the central nervous system. Despite efficacy in a mouse model of inflammatory bowel disease (IBD), a randomized controlled trial examining the effect of CBD in IBD patients did not identify any change in disease severity [64]. However, a phase II clinical trial investigating the use of adjunctive CBD to prevent graft-versus-host disease (GVHD) found CBD may be a useful adjunctive medication to standard immunosuppressive therapies [65].

In sum, evidence suggests that CBD may prove to be a valid therapeutic option for several conditions, though many areas thought to be particularly promising have shown mixed results, emphasizing that further research will need to investigate the therapeutic effects of CBD in rigorous clinical studies.

4.2. Adverse effects

As opposed to THC, which may cause several acute and chronic adverse effects, CBD is notable for having a comparably good safety profile. Most notably, as CBD does not agonize CB1 receptors, it is devoid of the psychotropic side effects associated with THC [17]. Reported short-term side effects of CBD use include somnolence, diarrhea, fatigue, and anorexia [15]. Additionally, there is evidence from animal

studies that CBD may inhibit several cytochrome P450 proteins, raising a possible concern for patients on medications dependent on hepatic metabolism [66–68]. Evidence suggests that CBD, through interactions with the 3A4 and 2C19 P450 isozymes, increases blood levels of clobazam, and has been found to alter blood levels of several other antiepileptics [20,69]. Given that CBD also has been found to interact with the p-glycoprotein drug transporters, it is very possible that other, currently unknown drug interactions exist [20]. Lastly, one notable indirect adverse effect from a public health perspective is that off-label use of CBD may preclude patients receiving evidence-based treatments.

Notably, studies examining the abuse potential of CBD have not identified any evidence of tolerance or physical dependence [15]. Indeed, some have even suggested that CBD's ability to therapeutically modulate dopaminergic neurotransmission in the mesolimbic pathway supports its role as a treatment for other substance use disorders [70]. Due to these findings, a World Health Organization report recommended that CBD not be labeled as a scheduled substance [15].

5. Conclusion

The medicalization of cannabis and cannabinoids presents several opportunities as well as challenges for medical professionals. From the perspective of researchers, studying cannabis is complicated by inadequate blinding, limited funding, charged political views, stigma, complicated legal status, and lack of standardization [38,71]. Clinicians attempting to safely use these substances for their patients encounter many of these issues as well as misinformed patients and an ever-evolving base of literature pointing to possible therapeutic indications. To sort through these possible indications, however, physicians and researchers should both expect the gold standard of randomized, double-blind, placebo-controlled clinical trials.

Whether under medical guidance or self-prescribed, patients will continue use these substances. In either case, physicians will need to be prepared to educate patients regarding the risks and benefits of these compounds. As the use and ubiquity of these substances continues to grow, the need to distinguish between high-quality clinical evidence, potentially promising preclinical data, and mere conjecture will only grow more important.

In the meantime, clinicians are best served by adhering to FDA-approved indications for CBD- and THC-based medications and restricting the use of medical cannabis to those few conditions supported by robust clinical data (such as pain or spasticity related to MS and possibly other forms of chronic pain). All patients being considered for these medications should undergo a thorough and complete medical and psychiatric evaluation to identify possible contraindications and should be followed if a cannabinoid-based medication is started.

Declarations of Competing Interest

None.

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THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

COMMITTEE'S CONCLUSIONS

January 2017

In the report The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research, an expert, ad hoc committee of the National Academies of Sciences, Engineering, and Medicine presents nearly 100 conclusions related to the health effects of cannabis and cannabinoid use.

The committee developed standard language to categorize the weight of the evidence regarding whether cannabis or cannabinoids used for therapeutic purposes are an effective or ineffective treatment for certain prioritized health conditions, or whether cannabis or cannabinoids used primarily for recreational purposes are statistically associated with certain prioritized health conditions. The box on the next page describes these categories and the general parameters for the types of evidence supporting each category.

The numbers in parentheses after each conclusion correspond to chapter conclusion numbers. Each blue header below links to the corresponding chapter in the report, providing much more detail regarding the committee's findings and conclusions. To read the full report, please visit **nationalacademies.org/CannabisHealthEffects.**

CONCLUSIONS FOR: THERAPEUTIC EFFECTS

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

For the treatment for chronic pain in adults (cannabis) (4-1)
Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

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

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

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

Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
Improving symptoms of Tourette syndrome (THC capsules) (4-8)
Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
Improving symptoms of posttraumatic stress disorder (nabilone; one single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are ineffective for:

Improving symptoms associated with dementia (cannabinoids) (4-13)
Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

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DEFINITIONS OF WEIGHTS OF EVIDENCE

The committee used the following standardized language to categorize the weight of the evidence regarding cannabis or cannabinoid use for the prioritized health conditions:

CONCLUSIVE EVIDENCE:

FOR THERAPEUTIC EFFECTS: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

FOR OTHER HEALTH EFFECTS: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE:

FOR THERAPEUTIC EFFECTS: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

FOR OTHER HEALTH EFFECTS: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE:

FOR THERAPEUTIC EFFECTS: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

FOR OTHER HEALTH EFFECTS: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several findings from good-to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE:

FOR THERAPEUTIC EFFECTS: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

FOR OTHER HEALTH EFFECTS: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION:

FOR THERAPEUTIC EFFECTS: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

FOR OTHER HEALTH EFFECTS: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

THERE IS NO OR INSUFFICIENT EVIDENCE TO SUPPORT OR REFUTE THE CONCLUSION THAT CANNABIS OR CANNABINOIDS ARE AN EFFECTIVE TREATMENT FOR:

Cancers, including glioma (cannabinoids) (4-2)

Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)

Symptoms of irritable bowel syndrome (dronabinol) (4-5)

Epilepsy (cannabinoids) (4-6)

Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)

Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)

Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)

Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)

Dystonia (nabilone and dronabinol) (4-12)

Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)

Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

CONCLUSIONS FOR: CANCER

THERE IS MODERATE EVIDENCE OF NO STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

THERE IS LIMITED EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS SMOKING AND:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

THERE IS NO OR INSUFFICIENT EVIDENCE TO SUPPORT OR REFUTE A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- \Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

CONCLUSIONS FOR: CARDIOMETABOLIC RISK

THERE IS LIMITED EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

THERE IS NO EVIDENCE TO SUPPORT OR REFUTE A STATISTICAL ASSOCIATION BETWEEN CHRONIC EFFECTS OF CANNABIS USE AND:

- The increased risk of acute myocardial infarction (6-1b)

CONCLUSIONS FOR: RESPIRATORY DISEASE

THERE IS SUBSTANTIAL EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS SMOKING AND:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

THERE IS MODERATE EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS SMOKING AND:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

THERE IS MODERATE EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN THE CESSATION OF CANNABIS SMOKING AND:

Improvements in respiratory symptoms (7-3b)

THERE IS LIMITED EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS SMOKING AND:

An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking

AND:

Hospital admissions for COPD (7-2b)

Asthma development or asthma exacerbation (7-4)

CONCLUSIONS FOR: IMMUNITY

THERE IS LIMITED EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS SMOKING AND:

A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of no statistical association between cannabis use and:

The progression of liver fibrosis or hepatic disease in individuals with viral Hepatitis C (HCV) (daily cannabis use) (8-3)

THERE IS NO OR INSUFFICIENT EVIDENCE TO SUPPORT OR REFUTE A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)

Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)

Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

CONCLUSIONS FOR: INJURY AND DEATH

THERE IS SUBSTANTIAL EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

Increased risk of motor vehicle crashes (9-3)

THERE IS MODERATE EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

THERE IS NO OR INSUFFICIENT EVIDENCE TO SUPPORT OR REFUTE A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

All-cause mortality (self-reported cannabis use) (9-1)

Occupational accidents or injuries (general, non-medical cannabis use) (9-2)

Death due to cannabis overdose (9-4a)

CONCLUSIONS FOR: PRENATAL, PERINATAL, AND NEONATAL EXPOSURE

THERE IS SUBSTANTIAL EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN MATERNAL CANNABIS SMOKING AND:

Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

Pregnancy complications for the mother (10-1)

Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

THERE IS INSUFFICIENT EVIDENCE TO SUPPORT OR REFUTE A STATISTICAL ASSOCIATION BETWEEN MATERNAL CANNABIS SMOKING AND:

Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

CONCLUSIONS FOR: PSYCHOSOCIAL

THERE IS MODERATE EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

THERE IS LIMITED EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

Impaired academic achievement and education outcomes (11-2)

Increased rates of unemployment and/or low income (11-3)

Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

THERE IS LIMITED EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN SUSTAINED ABSTINENCE FROM CANNABIS USE AND:

Impairments in the cognitive domains of learning, memory, and attention (11-1b)

CONCLUSIONS FOR: MENTAL HEALTH

THERE IS SUBSTANTIAL EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

THERE IS MODERATE EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)

Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)

A small increased risk for the development of depressive disorders (12-5)

Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)

Increased incidence of suicide completion (12-7b)

Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

THERE IS MODERATE EVIDENCE OF NO STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)

The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)

The development of any type of anxiety disorder, except social anxiety disorder (12-8a)

Increased symptoms of anxiety (near daily cannabis use) (12-9)

Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

THERE IS NO EVIDENCE TO SUPPORT OR REFUTE A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

Changes in the course or symptoms of depressive disorders (12-6)

The development of posttraumatic stress disorder (12-10)

CONCLUSIONS FOR: PROBLEM CANNABIS USE

THERE IS SUBSTANTIAL EVIDENCE THAT:

Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is not a risk factor for the development of problem cannabis use (13-2e)

Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)

Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

THERE IS SUBSTANTIAL EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN:

Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)

Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

THERE IS MODERATE EVIDENCE THAT:

Anxiety, personality disorders, and bipolar disorders are not risk factors for the development of problem cannabis use (13-2b)

Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)

Adolescent ADHD is not a risk factor for the development of problem cannabis use (13-2d)

Being male is a risk factor for the development of problem cannabis use (13-2f)

Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)

Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)

During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

THERE IS MODERATE EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN:

A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)

Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

THERE IS LIMITED EVIDENCE THAT:

Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

CONCLUSIONS FOR: ABUSE OF OTHER SUBSTANCES

THERE IS MODERATE EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

The development of substance dependence and/or substance abuse disorder for substances including alcohol, tobacco, and other illicit drugs (14-3)

THERE IS LIMITED EVIDENCE OF A STATISTICAL ASSOCIATION BETWEEN CANNABIS USE AND:

The initiation of tobacco use (14-1)

Changes in the rates and use patterns of other licit and illicit substances (14-2)

CONCLUSIONS FOR: CHALLENGES AND BARRIERS IN CONDUCTING CANNABIS AND CANNABINOID RESEARCH

THERE ARE SEVERAL CHALLENGES AND BARRIERS IN CONDUCTING CANNABIS AND CANNABINOID RESEARCH, INCLUDING:

There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)

It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)

A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful effects of cannabis use (15-3)

To develop conclusive evidence for the effects of cannabis use for short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

TO READ THE FULL REPORT AND VIEW RELATED RESOURCES, PLEASE VISIT NATIONALACADEMIES.ORG/CANNABISHEALTHEFFECTS

Role of Cannabinoids in Pain Management

18

Ethan B. Russo and Andrea G. Hohmann

Key Points

- Cannabinoids are pharmacological agents of endogenous (endocannabinoids), botanical (phytocannabinoids), or synthetic origin.
- Cannabinoids alleviate pain through a variety of receptor and non-receptor mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.
- Cannabinoid agents are currently available in various countries for pain treatment, and even cannabinoids of botanical origin may be approvable by FDA, although this is distinctly unlikely for smoked cannabis.
- An impressive body of literature supports cannabinoid analgesia, and recently, this has been supplemented by an increasing number of phase I–III clinical trials.

Introduction

Plants and Pain

It is a curious fact that we owe a great deal of our insight into pharmacological treatment of pain to the plant world [1]. Willow bark from *Salix* spp. led to development of aspirin and eventual elucidation of the analgesic effects of prostaglandins and their role in inflammation. The opium poppy (*Papaver somniferum*) provided the prototypic narcotic analgesic morphine, the first alkaloid discovered, and stimulated the much later discovery of the endorphin and enkephalin systems. Similarly, the pharmacological properties of cannabis (*Cannabis sativa*) prompted the isolation of Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, in 1964 [2]. It is this breakthrough that subsequently prompted the more recent discovery of the body's own cannabis-like system, the endocannabinoid system (ECS), which modulates pain under physiological conditions. Pro-nociceptive mechanisms of the endovanilloid system were similarly revealed by phytochemistry of capsaicin, the pungent ingredient in hot chile peppers (*Capsicum annuum* etc.), which activates transient receptor potential vanilloid receptor-1 (TRPV1). Additional plant products such as the mints and mustards activate other TRP channels to produce their physiological effects.

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The Endocannabinoid System

There are three recognized types of cannabinoids: (1) the phytocannabinoids [3] derived from the cannabis plant, (2) synthetic cannabinoids (e.g., ajulemic acid, nabilone, CP55940, WIN55, 212-2) based upon the chemical structure of THC or other ligands which bind cannabinoid receptors, and (3) the endogenous cannabinoids or endocannabinoids. Endocannabinoids are natural chemicals such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) found in animals whose basic functions are "relax, eat, sleep, forget, and protect" [4]. The endocannabinoid system encompasses the endocannabinoids themselves, their biosynthetic and catabolic enzymes, and their corresponding receptors [5]. AEA is hydrolyzed by the enzyme fatty-acid amide hydrolase (FAAH) into breakdown products arachidonic acid and ethanolamine [6]. By contrast, 2-AG is hydrolyzed primarily by the enzyme monoacylglycerol lipase (MGL) into breakdown products arachidonic acid and glycerol [7] and to a lesser extent by the enzymes ABHD6 and ABHD12. FAAH, a

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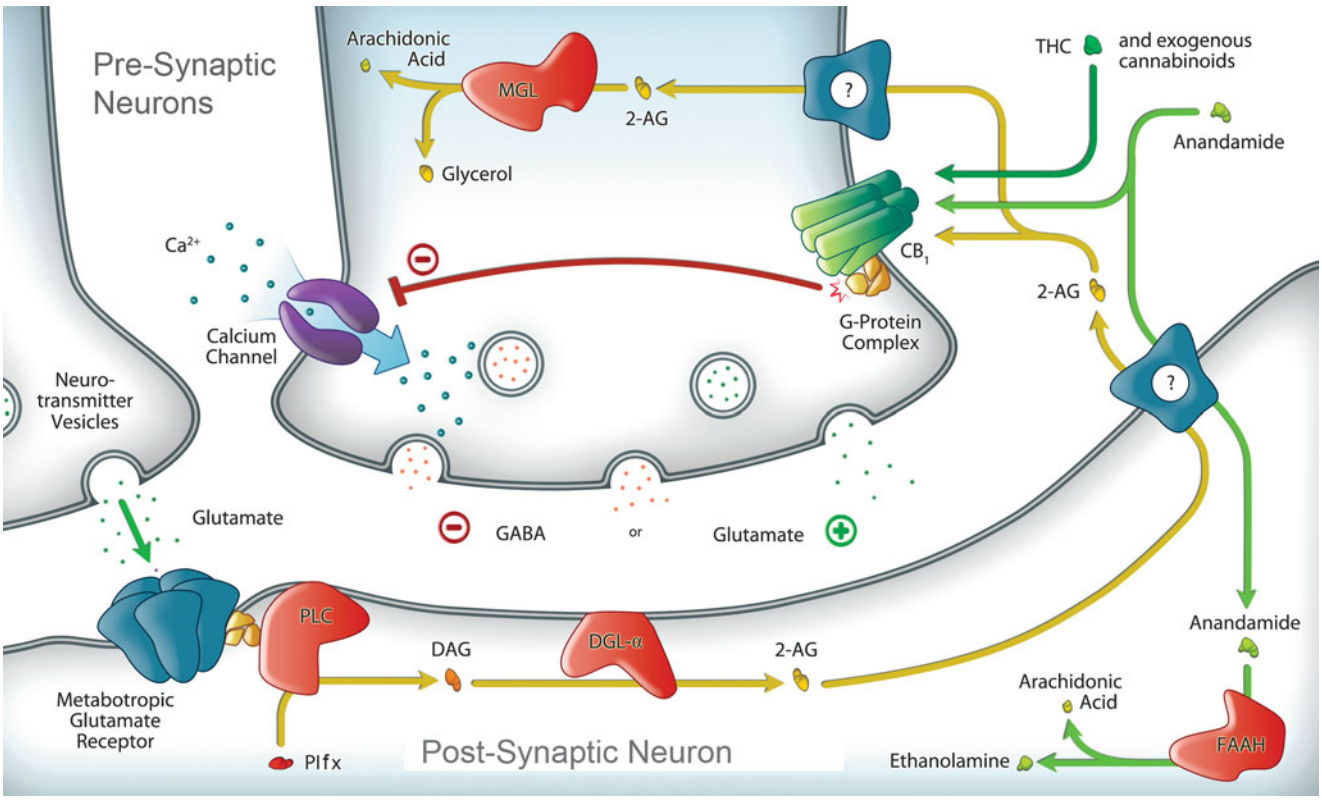

Fig. 18.1 Putative mechanism of endocannabinoid-mediated retrograde signaling in the nervous system. Activation of metabotropic glutamate receptors (*mGluR*) by glutamate triggers the activation of the phospholipase C (*PLC*)-diacylglycerol lipase (*DGL*) pathway to generate the endocannabinoid 2-arachidonoylglycerol (*2-AG*). First, the 2-AG precursor diacylglycerol (*DAG*) is formed from PLC-mediated hydrolysis of membrane phospholipid precursors (*PIPx*). DAG is then hydrolyzed by the enzyme DGL-α to generate 2-AG. 2-AG is released from the postsynaptic neuron and acts as a retrograde signaling molecule. Endocannabinoids activate presynaptic CB_1 receptors which reside on terminals of glutamatergic and GABAergic neurons. Activation of CB_1 by 2-AG, anandamide, or exogenous cannabinoids (e.g., tetrahydrocannabinol, *THC*) inhibits calcium influx in the presynaptic terminal, thereby inhibiting release of the primary neurotransmitter (i.e., glutamate or GABA) from the synaptic vesicle. Endocannabinoids are then rapidly deactivated by transport into cells (via a putative endocannabinoid transporter) followed by intracellular hydrolysis. 2-AG is metabolized by the enzyme monoacylglycerol lipase (*MGL*), whereas anandamide is metabolized by a distinct enzyme, fatty-acid amide hydrolase (*FAAH*). Note that MGL co-localizes with CB_1 in the presynaptic terminal, whereas FAAH is localized to postsynaptic sites. The existence of an endocannabinoid transporter remains controversial. Pharmacological inhibitors of either endocannabinoid deactivation (e.g., FAAH and MGL inhibitors) or transport (i.e., uptake inhibitors) have been developed to exploit the therapeutic potential of the endocannabinoid signaling system in the treatment of pain (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

postsynaptic enzyme, may control anandamide levels near sites of synthesis, whereas MGL, a presynaptic enzyme [8], may terminate 2-AG signaling following CB_1 receptor activation. These enzymes also represent therapeutic targets because inhibition of endocannabinoid deactivation will increase levels of endocannabinoids at sites with ongoing synthesis and release [9]. The pathways controlling formation of AEA remain poorly understood. However, 2-AG is believed to be formed from membrane phospholipid precursors through the sequential activation of two distinct enzymes, phospholipase C and diacylglycerol lipase-α. First, PLC catalyzes formation of the 2-AG precursor diacylglycerol (DAG) from membrane phosphoinositides. Then, DAG is hydrolyzed by the enzyme diacylglycerol lipase-α (DGL-α) to generate 2-AG [199].

There are currently two well-defined cannabinoid receptors, although additional candidate cannabinoid receptors have also been postulated. CB_1, a seven transmembrane spanning G-protein-coupled receptor inhibiting cyclic AMP release, was identified in 1988 [10]. CB_1 is the primary neuromodulatory receptor accounting for psychopharmacological effects of THC and most of its analgesic effects [11]. Endocannabinoids are produced on demand in postsynaptic cells and engage presynaptic CB_1 receptors through a retrograde mechanism [12]. Activation of presynaptic CB_1 receptors then acts as a synaptic circuit breaker to inhibit neurotransmitter release (either excitatory or inhibitory) from the presynaptic neuron (*vide infra*) (Fig. 18.1). CB_2 was identified in 1992, and while thought of primarily as a peripheral immunomodulatory receptor, it also has important

effects on pain. The role of CB_2 in modulating persistent inflammatory and neuropathic pain [13] has been recently reviewed [14, 15]. Activation of CB_2 suppresses neuropathic pain mechanisms through nonneuronal (i.e., microglia and astrocytes) and neuronal mechanisms that may involve interferon-gamma [16]. THC, the prototypical classical cannabinoid, is a weak partial agonist at both CB_1 and CB_2 receptors. Transgenic mice lacking cannabinoid receptors (CB_1, CB_2, GPR55), enzymes controlling endocannabinoid breakdown (FAAH, MGL, ABHD6), and endocannabinoid synthesis (DGL-α, DGL-β) have been generated [17]. These knockouts have helped elucidate the role of the endocannabinoid system in controlling nociceptive processing and facilitated development of inhibitors of endocannabinoid breakdown (FAAH, MGL) as novel classes of analgesics.

A Brief Scientific History of Cannabis and Pain

Centuries of Citations

Cannabis has been utilized in one form or another for treatment of pain for longer than written history [18–21]. Although this documentation has been a major preoccupation of the lead author [22–25], and such information can provide provocative direction to inform modern research on treatment of pain and other conditions, it does not represent evidence of form, content, or degree that is commonly acceptable to governmental regulatory bodies with respect to pharmaceutical development.

Anecdotes Versus Modern Proof of Concept

While thousands of compelling stories of efficacy of cannabis in pain treatment certainly underline the importance of properly harnessing cannabinoid mechanisms therapeutically [26, 27], prescription analgesics in the United States necessitate Food and Drug Administration (FDA) approval. This requires a rigorous development program proving consistency, quality, efficacy, and safety as defined by basic scientific studies and randomized controlled trials (RCT) [28] and generally adhering to recent IMMPACT recommendations [29], provoking our next question.

Can a Botanical Agent Become a Prescription Medicine?

Most modern physicians fail to recognize that pharmacognosy (study of medicinal plants) has led directly or indirectly to an estimated 25 % of modern pharmaceuticals [30]. While the plethora of available herbal agents yield an indecipherable cacophony to most clinicians and consumers alike, it is certainly possible to standardize botanical agents and facilitate their recommendation based on sound science [31]. Botanical medicines can even fulfill the rigorous dictates of the FDA and attain prescription drug status via a clear roadmap in the form of a blueprint document [32], henceforth termed the *Botanical Guidance*: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf. To be successful and clinically valuable, botanicals, including cannabis-based medicines, must demonstrate the same quality, clinical analgesic benefit, and appropriately safe adverse event profile as available new chemical entities (NCE) [28].

The Biochemical and Neurophysiological Basis of Pain Control by Cannabinoids

Neuropathic Pain

Thorough reviews of therapeutic effects of cannabinoids in preclinical and clinical domains have recently been published [33, 34]. In essence, the endocannabinoid system (ECS) is active throughout the CNS and PNS in modulating pain at spinal, supraspinal, and peripheral levels. Endocannabinoids are produced on demand in the CNS to dampen sensitivity to pain [35]. The endocannabinoid system is operative in such key integrative pain centers as the periaqueductal grey matter [36, 37], the ventroposterolateral nucleus of the thalamus [38], and the spinal cord [39, 40]. Endocannabinoids are endogenous mediators of stress-induced analgesia and fear-conditioned analgesia and suppress pain-related phenomena such as windup [41] and allodynia [42]. In the periphery and PNS [13], the ECS has key effects in suppressing both hyperalgesia and allodynia via CB_1 [43] and CB_2 mechanisms (Fig. 18.2). Indeed, pathological pain states have been postulated to arise, at least in part, from a dysregulation of the endocannabinoid system.

Antinociceptive and Anti-inflammatory Pain Mechanisms

Beyond the mechanisms previously mentioned, the ECS plays a critical role in peripheral pain, inflammation, and hyperalgesia [43] through both CB_1 and CB_2 mechanisms. CB_1 and CB_2 mechanisms are also implicated in regulation of contact dermatitis and pruritus [44]. A role for spinal CB_2 mechanisms, mediated by microglia and/or astrocytes, is also revealed under conditions of inflammation [45]. Both THC and cannabidiol (CBD), a non-euphoriant phytocannabinoid common in certain cannabis strains, are potent anti-inflammatory antioxidants with activity exceeding that of

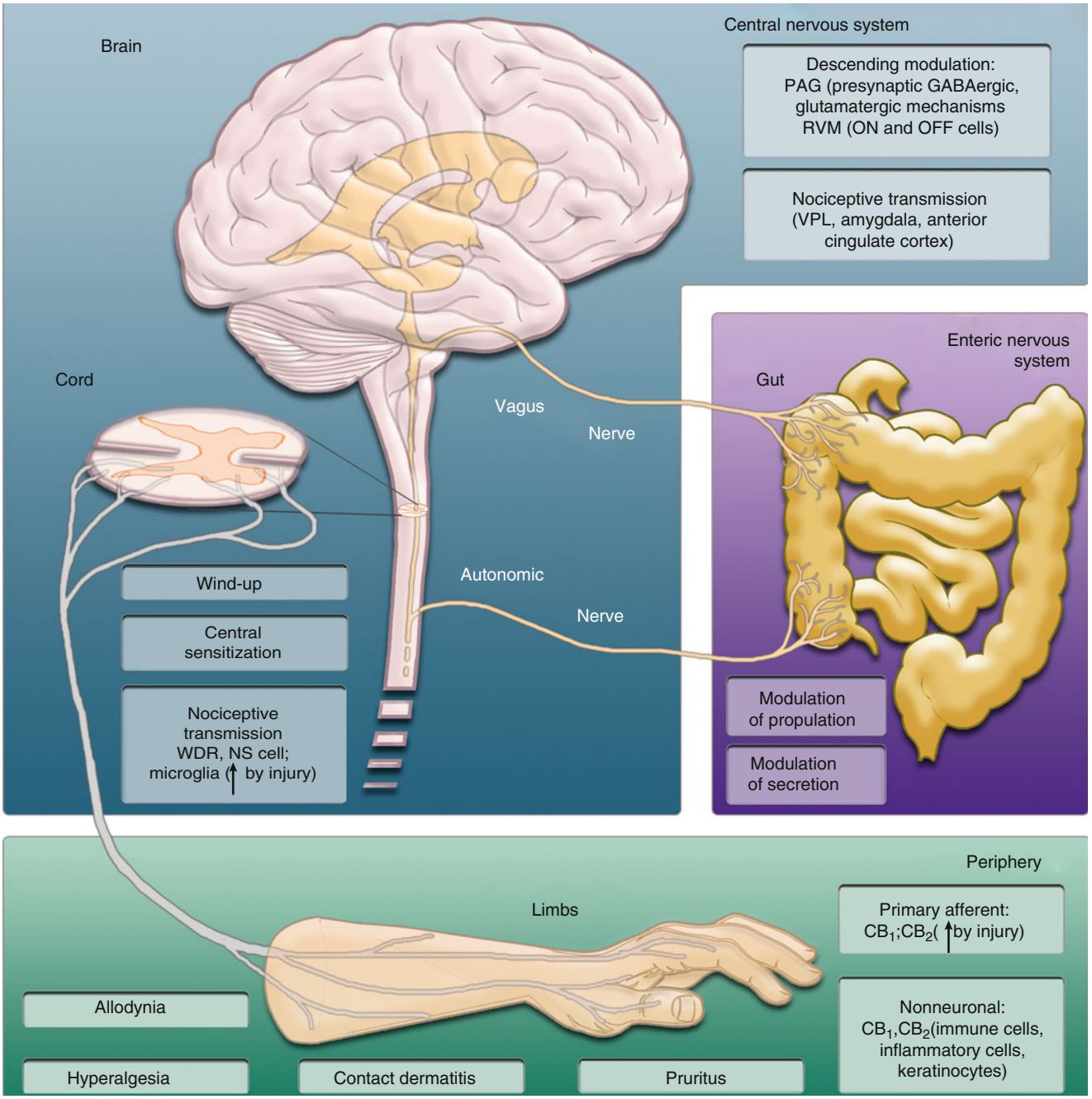

Fig. 18.2 Cannabinoids suppress pain and other pathophysiological (e.g., contact dermatitis, pruritis) and physiological (e.g., gastrointestinal transit and secretion) processes through multiple mechanisms involving CB_1 and CB_2 receptors. Peripheral, spinal, and supraspinal sites of cannabinoid actions are shown. In the periphery, cannabinoids act through both neuronal and nonneuronal mechanisms to control inflammation, allodynia, and hyperalgesia. CB_1 and CB_2 have been localized to both primary afferents and nonneuronal cells (e.g., keratinocytes, microglia), and expression can be regulated by injury. In the spinal cord, cannabinoids suppress nociceptive transmission, windup, and central sensitization by modulating activity in the ascending pain pathway of the spinothalamic tract, including responses of wide dynamic range (*WDR*) and nociceptive specific (*NS*) cells. Similar processes are observed at rostral levels of the neuraxis (e.g., ventroposterolateral nucleus of the thalamus, amygdala, anterior cingulate cortex). Cannabinoids also actively modulate pain through descending mechanisms. In the periaqueductal gray, cannabinoids act through presynaptic glutamatergic and GABAergic mechanisms to control nociception. In the rostral ventromedial medulla, cannabinoids suppress activity in ON cells and inhibit the firing pause of OFF cells, in response to noxious stimulation to produce antinociception (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

vitamins C and E via non-cannabinoid mechanisms [46]. THC inhibits prostaglandin E-2 synthesis [47] and stimulates lipooxygenase [48]. Neither THC nor CBD affects COX-1 or COX-2 at relevant pharmacological dosages [49].

While THC is inactive at vanilloid receptors, CBD, like AEA, is a $TRPV_1$ agonist. Like capsaicin, CBD is capable of inhibiting fatty-acid amide hydrolase (FAAH), the enzyme which hydrolyzes AEA and other fatty-acid amides that do not bind to cannabinoid receptors. CBD additionally inhibits AEA reuptake [50] though not potently. Thus, CBD acts as an endocannabinoid modulator [51], a mechanism that various pharmaceutical firms hope to emulate with new chemical entities (NCEs). CBD inhibits hepatic metabolism of THC to 11-hydroxy-THC, which is possibly more psychoactive, and prolongs its half-life, reducing its psychoactivity and attenuating attendant anxiety and tachycardia [51]; antagonizes psychotic symptoms [52]; and attenuates appetitive effects of THC [53] as well as its effects on short-term memory [54]. CBD also inhibits tumor necrosis factor-alpha (TNF-α) in a rodent model of rheumatoid arthritis [55]. Recently, CBD has been demonstrated to enhance adenosine receptor A2A signaling via inhibition of the adenosine transporter [56].

Recently, GPR18 has been proposed as a putative CBD receptor whose function relates to cellular migration [57]. Antagonism of GPR18 (by agents such as CBD) may be efficacious in treating pain of endometriosis, among other conditions, especially considering that such pain may be endocannabinoid-mediated [58]. Cannabinoids are also very active in various gastrointestinal and visceral sites mediating pain responses [59, 60].

Cannabinoid Interactions with Other Neurotransmitters Pertinent to Pain

As alluded to above, the ECS modulates neurotransmitter release via retrograde inhibition. This is particularly important in NMDA-glutamatergic mechanisms that become hyperresponsive in chronic pain states. Cannabinoids specifically inhibit glutamate release in the hippocampus [61]. THC reduces NMDA responses by 30–40 % [46]. Secondary and tertiary hyperalgesia mediated by NMDA [62] and by calcitonin gene-related peptide [40] may well be targets of cannabinoid therapy in disorders such as migraine, fibromyalgia, and idiopathic bowel syndrome wherein these mechanisms seem to operate pathophysiologically [63], prompting the hypothesis of a "clinical endocannabinoid deficiency." Endocannabinoid modulators may therefore restore homeostasis, leading to normalization of function in these pathophysiological conditions. THC also has numerous effects on serotonergic systems germane to migraine [64], increasing its production in the cerebrum while decreasing reuptake [65]. In fact, the ECS seems to modulate the trigeminovascular system of migraine pathogenesis at vascular and neurochemical levels [66–68].

Cannabinoid-Opioid Interactions

Although endocannabinoids do not bind to opioid receptors, the ECS may nonetheless work in parallel with the endogenous opioid system with numerous areas of overlap and interaction. Pertinent mechanisms include stimulation of beta-endorphin by THC [69] as well as its ability to demonstrate experimental opiate sparing [70], prevent opioid tolerance and withdrawal [71], and rekindle opioid analgesia after loss of effect [72]. Adjunctive treatments that combine opioids with cannabinoids may enhance the analgesic effects of either agent. Such strategies may permit lower doses of analgesics to be employed for therapeutic benefit in a manner that minimizes incidence or severity of adverse side effects.

Clinical Trials, Utility, and Pitfalls of Cannabinoids in Pain

Evidence for Synthetic Cannabinoids

Oral dronabinol (THC) has been available as the synthetic Marinol® since 1985 and is indicated for nausea associated with chemotherapy and appetite stimulation in HIV/AIDS. Issues with its cost, titration difficulties, delayed onset, and propensity to induce intoxicating and dysphoric effects have limited clinical application [73]. It was employed in two open-label studies of chronic neuropathic pain in case studies in 7 [74] and 8 patients [75], but no significant benefit was evident and side effects led to prominent dropout rates (average doses 15–16.6 mg THC). Dronabinol produced benefit in pain in multiple sclerosis [76], but none was evident in postoperative pain (Table 18.1) [77]. Dronabinol was reported to relieve pruritus in three case-report subjects with cholestatic jaundice [78]. Dronabinol was assessed in 30 chronic noncancer pain patients on opioids in double-blind crossover single-day sessions vs. placebo with improvement [79], followed by a 4-week open-label trial with continued improvement (Table 18.1). Associated adverse events were prominent. Methodological issues included lack of prescreening for cannabinoids, 4 placebo subjects with positive THC assays, and 58 % of subjects correctly guessing Marinol dose on test day. An open-label comparison in polyneuropathy examined nabilone patients with 6 obtaining 22.6 % mean pain relief after 3 months, and 5 achieving 28.6 % relief after 6 months, comparable to conventional agents [80]. A pilot study of Marinol in seven spinal cord injury patients with neuropathic pain saw two withdraw, and the remainder appreciate no greater efficacy than with diphenhydramine [81].

Table 18.1 Randomized controlled trials of cannabinoids in pain

Agent	*N*=	Indication	Duration/type	Outcomes/reference
Ajulemic acid	21	Neuropathic pain	7 day crossover	Visual analogue pain scales improved over placebo ($p=0.02$)/Karst et al. [92]
Cannabis, smoked	50	HIV neuropathy	5 days/DB	Decreased daily pain ($p=0.03$) and hyperalgesia ($p=0.05$), 52 % with >30 % pain reduction vs. placebo ($p=0.04$)/Abrams et al. [94]
Cannabis, smoked	23	Chronic neuropathic pain	5 days/DB	Decreased pain vs. placebo only at 9.4 % THC level ($p=0.023$)/Ware et al. [98]
Cannabis, smoked	38	Neuropathic pain	Single dose/DBC	NSD in pain except at highest cannabis dose ($p=0.02$), with prominent psychoactive effects/Wilsey et al. [95]
Cannabis, smoked	34	HIV neuropathy	5 days /DB	DDS improved over placebo ($p=0.016$), 46 % vs. 18 % improved >30 %, 2 cases toxic psychosis/Ellis et al. [97]
Cannabis, vaporized	21	Chronic pain on opioids	5 days/DB	27 % decrement in pain/Abrams et al. [118]
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. [120]
Cannador	65	Postherpetic neuralgia	4 weeks	No benefit observed/Ernst et al. [122]
Cannador	30	Postoperative pain	Single doses, daily	Decreasing pain intensity with increased dose ($p=0.01$)/Holdcroft et al. [123]
Marinol	24	Neuropathic pain in MS	15–21 days/DBC	Median numerical pain ($p=0.02$), median pain relief improved ($p=0.035$) over placebo/Svendsen et al. [76]
Marinol	40	Postoperative pain	Single dose/DB	No benefit observed over placebo/Buggy et al. [77]
Marinol	30	Chronic pain	3 doses, 1 day/DBC	Total pain relief improved with 10 mg ($p<0.05$) and 20 mg ($p<0.01$) with opioids, AE prominent/Narang et al. [79]
Nabilone	41	Postoperative pain	3 doses in 24 h/DB	NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg/Beaulieu [85]
Nabilone	31	Fibromyalgia	2 weeks/DBC	Compared to amitriptyline, nabilone improved sleep, decrease wakefulness, had no effect on pain, and increased AE/Ware et al. [90]
Nabilone	96	Neuropathic pain	14 weeks/DBC vs. dihydrocodeine	Dihydrocodeine more effective with fewer AE/Frank et al. [88]
Nabilone	13	Spasticity pain	9 weeks/DBC	NRS decreased 2 points for nabilone ($p<0.05$)/Wissel et al. [87]
Nabilone	40	Fibromyalgia	4 weeks/DBC	VAS decreased in pain, Fibromyalgia Impact Questionnaire, and anxiety over placebo (all, $p<0.02$)/Skrabek et al. [89]
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. [132]
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. [133]
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. [134]
Sativex	66	Central neuropathic pain in MS	5 weeks	Numerical Rating Scale (NRS) analgesia improved over placebo ($p=0.009$)/Rog et al. [135]

(continued)

Table 18.1 (continued)

Agent	*N*=	Indication	Duration/type	Outcomes/reference
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. [136]
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 ($p=0.002$), and SF-MPQ pain at present ($p=0.016$)/Blake et al. [138]
Sativex	117	Pain after spinal injury	10 days	NSD in NRS pain scores, 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 et al. [139]
Sativex	135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo ($p=0.001$) [200]
Sativex	360	Intractable cancer pain	5 weeks/DB	CRA of lower and middle-dose cohorts improved over placebo ($p=0.006$)/ [201]

Nabilone, or Cesamet®, is a semisynthetic analogue of THC that is about tenfold more potent, and longer lasting [82]. It is indicated as an antiemetic in chemotherapy in the USA. Prior case reports in neuropathic pain [83] and other pain disorders [84] have been published. Sedation and dysphoria are prominent associated adverse events. An RCT of nabilone in 41 postoperative subjects dosed TID actually resulted in increased pain scores (Table 18.1) [85]. An uncontrolled study of 82 cancer patients on nabilone noted improved pain scores [86], but retention rates were limited. Nabilone improved pain ($p<0.05$) vs. placebo in patients with mixed spasticity syndromes in a small double-blind trial (Table 18.1) [87], but was without benefits in other parameters. In a double-blind crossover comparison of nabilone to dihydrocodeine (schedule II opioid) in chronic neuropathic pain (Table 18.1) [88], both drugs produced marginal benefit, but with dihydrocodeine proving clearly superior in efficacy and modestly superior in side-effect profile. In an RCT in 40 patients of nabilone vs. placebo over 4 weeks, it showed significant decreases in VAS of pain and anxiety (Table 18.1) [89]. A more recent study of nabilone vs. amitriptyline in fibromyalgia yielded benefits on sleep, but not pain, mood, or quality of life (Table 18.1) [90]. An open-label trial of nabilone vs. gabapentin found them comparable in pain and other symptom relief in peripheral neuropathic pain [91].

Ajulemic acid (CT3), another synthetic THC analogue in development, was utilized in a phase II RCT in peripheral neuropathic pain in 21 subjects with apparent improvement (Table 18.1) [92]. Whether or not ajulemic acid is psychoactive is the subject of some controversy [93].

Evidence for Smoked or Vaporized Cannabis

Few randomized controlled clinical trials (RCTs) of pain with smoked cannabis have been undertaken to date [94–97]. One of these [96] examined cannabis effects on experimental pain in normal volunteers.

Abrams et al. [94] studied inpatient adults with painful HIV neuropathy in 25 subjects in double-blind fashion to receive either smoked cannabis as 3.56 % THC cigarettes or placebo cigarettes three times daily for 5 days (Table 18.1). The smoked cannabis group had a 34 % reduction in daily pain vs. 17 % in the placebo group ($p=0.03$). The cannabis cohort also had a 52 % of subjects report a >30 % reduction in pain scores over the 5 days vs. 24 % in the placebo group ($p=0.04$) (Table 18.1). The authors rated cannabis as "well tolerated" due to an absence of serious adverse events (AE) leading to withdrawal, but all subjects were cannabis experienced. Symptoms of possible intoxication in the cannabis group including anxiety (25 %), sedation (54 %), disorientation (16 %), paranoia (13 %), confusion (17 %), dizziness (15 %), and nausea (11 %) were all statistically significantly more common than in the placebo group. Despite these findings, the authors stated that the values do not represent any serious safety concern in this short-term study. No discussion in the article addressed issues of the relative efficacy of blinding in the trial.

Wilsey et al. [95] examined neuropathic pain in 38 subjects in a double-blind crossover study comparing 7 % THC cannabis, 3.5 % THC cannabis, and placebo cigarettes via a complex cumulative dosing scheme with each dosage given

once, in random order, with at least 3 day intervals separating sessions (Table 18.1). A total of 9 puffs maximum were allowed over several hours per session. Authors stated, "Psychoactive effects were minimal and well-tolerated, but neuropsychological impairment was problematic, particularly with the higher concentration of study medication." Again, only cannabis-experienced subjects were allowed entry. No withdrawals due to AE were reported, but 1 subject was removed due to elevated blood pressure. No significant differences were noted in pain relief in the two cannabis potency groups, but a significant separation of pain reduction from placebo ($p=0.02$) was not evident until a cumulative 9 puffs at 240 min elapsed time. Pain unpleasantness was also reduced in both active treatment groups ($p<0.01$). Subjectively, an "any drug effect" demonstrated a visual analogue scale (VAS) of 60/100 in the high-dose group, but even the low-dose group registered more of a "good drug effect" than placebo ($p<0.001$). "Bad drug effect" was also evident. "Feeling high" and "feeling stoned" were greatest in the high-dose sessions ($p<0.001$), while both high- and low-dose differentiated significantly from placebo ($p<0.05$). Of greater concern, both groups rated impairment as 30/100 on VAS vs. placebo ($p=0.003$). Sedation also demarcated both groups from placebo ($p<0.01$), as did confusion ($p=0.03$), and hunger ($p<0.001$). Anxiety was not considered a prominent feature in this cannabis-experienced population. This study distinguished itself from some others in its inclusion of specific objective neuropsychological measures and demonstrated neurocognitive impairment in attention, learning, and memory, most noteworthy with 7 % THC cannabis. No commentary on blinding efficacy was included.

Ellis et al. [97] examined HIV-associated neuropathic pain in a double-blind trial of placebo vs. 1–8 % THC cannabis administered four times daily over 5 days with a 2-week washout (Table 18.1). Subjects were started at 4 % THC and then titrated upward or downward in four smoking sessions dependent upon their symptom relief and tolerance of the dose. In this study, 96 % of subjects were cannabis-experienced, and 28 out of 34 subjects completed the trial. The primary outcome measure (Descriptor Differential Scale, DDS) was improved in the active group over placebo ($p=0.016$), with >30 % relief noted in 46 % of cannabis subjects vs. 18 % of placebo. While most adverse events (AE) were considered mild and self-limited, two subjects had to leave the trial due to toxicity. One cannabis-naïve subject was withdrawn due to "an acute cannabis-induced psychosis" at what proved to be his first actual cannabis exposure. The other subject suffered intractable cough. Pain reduction was greater in the cannabis-treated group ($p=0.016$) among completers, as was the proportion of subjects attaining >30 % pain reduction (46 % vs. 18 %, $p=0.043$). Blinding was assessed in this study; whereas placebo patients were inaccurate at guessing the investigational product, 93 % of those receiving cannabis guessed correctly. On safety issues, the authors stated that the frequency of some nontreatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst.

A Canadian study [98] examined single 25-mg inhalations of various cannabis potencies (0–9.4 % THC) three times daily for 5 days per cycle in 23 subjects with chronic neuropathic pain (Table 18.1). Patients were said to be cannabis-free for 1 year, but were required to have some experience of the drug. Only the highest potency demarcated from placebo on decrements in average daily pain score (5.4 vs. 6.1, $p=0.023$). The most frequent AE in the high-dose group were headache, dry eyes, burning sensation, dizziness, numbness, and cough, but with "high" or "euphoria" reported only once in each cannabis potency group.

The current studies of smoked cannabis are noteworthy for their extremely short-term exposure and would be of uncertain relevance in a regulatory environment. The IMMPACT recommendations on chronic neuropathic pain clinical trials that are currently favored by the FDA [29] generally suggest randomized controlled clinical trials of 12-week duration as a prerequisite to demonstrate efficacy and safety. While one might assume that the degree of pain improvement demonstrated in these trials could be maintained over this longer interval, it is only reasonable to assume that cumulative adverse events would also increase to at least some degree. The combined studies represent only a total of 1,106 patient-days of cannabis exposure (Abrams: 125, Wilsey: 76, Ellis: 560, Ware 345) or 3 patient-years of experience. In contrast, over 6,000 patient-years of data have been analyzed for Sativex between clinical trials, prescription, and named-patient supplies, with vastly lower AE rates (data on file, GW Pharmaceuticals) [28, 99]. Certainly, the cognitive effects noted in California-smoked cannabis studies figure among many factors that would call the efficacy of blinding into question for investigations employing such an approach. However, it is also important to emphasize that unwanted side effects are not unique to cannabinoids. In a prospective evaluation of specific chronic polyneuropathy syndromes and their response to pharmacological therapies, the presence of intolerable side effects did not differ in groups receiving gabapentinoids, tricyclic antidepressants, anticonvulsants, cannabinoids (including nabilone, Sativex), and topical agents [80]. Moreover, no serious adverse events were related to any of the medications.

The current studies were performed in a very select subset of patients who almost invariably have had prior experience of cannabis. Their applicability to cannabis-naïve populations is, thus, quite unclear. At best, the observed benefits might possibly accrue to some, but it is eminently likely that candidates for such therapy might refuse it on any number of

grounds: not wishing to smoke, concern with respect to intoxication, etc. Sequelae of smoking in therapeutic outcomes have had little discussion in these brief RCTs [28]. Cannabis smoking poses substantial risk of chronic cough and bronchitic symptoms [100], if not obvious emphysematous degeneration [101] or increase in aerodigestive cancers [102]. Even such smoked cannabis proponents as Lester Grinspoon has acknowledged are the only well-confirmed deleterious physical effect of marihuana is harm to the pulmonary system [103]. However, population-based studies of cannabis trials have failed to show any evidence for increased risk of respiratory symptoms/chronic obstructive pulmonary disease [100] or lung cancer [102] associated with smoking cannabis.

A very detailed analysis and comparison of mainstream and sidestream smoke for cannabis vs. tobacco smoke was performed in Canada [104]. Of note, cannabis smoke contained ammonia (NH_3) at a level of 720 μg per 775 mg cigarette, a figure 20-fold higher than that found in tobacco smoke. It was hypothesized that this finding was likely attributable to nitrate fertilizers. Formaldehyde and acetaldehyde were generally lower in cannabis smoke than in tobacco, but butyraldehyde was higher. Polycyclic aromatic hydrocarbon (PAH) contents were qualitatively similar in the comparisons, but total yield was lower for cannabis mainstream smoke, but higher than tobacco for sidestream smoke. Additionally, NO, NO_x, hydrogen cyanide, and aromatic amines concentrations were 3–5 times higher in cannabis smoke than that from tobacco. Possible mutagenic and carcinogenic potential of these various compounds were mentioned. More recently, experimental analysis of cannabis smoke with resultant acetaldehyde production has posited its genotoxic potential to be attributable to reactions that produce DNA adducts [105].

Vaporizers for cannabis have been offered as a harm reduction technique that would theoretically eliminate products of combustion and associated adverse events. The Institute of Medicine (IOM) examined cannabis issues in 1999 [106], and among their conclusions was the following (p. 4): "Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems." One proposed technique is vaporization, whereby cannabis is heated to a temperature that volatilizes THC and other components with the goal of reducing or eliminating by-products of combustion, including potentially carcinogenic polycyclic aromatic hydrocarbons, benzene, acetaldehyde, carbon monoxide, toluene, naphthaline, phenol, toluene, hydrogen cyanide, and ammonia. Space limitations permit only a cursory review of available literature [107–115].

A pilot study of the Volcano vaporizer vs. smoking was performed in the USA in 2007 in 18 active cannabis consumers, with only 48 h of presumed abstinence [116]. NIDA 900-mg cannabis cigarettes were employed (1.7, 3.4, and 6.8 % THC) with each divided in two, so that one-half would be smoked or vaporized in a series of double-blind sessions. The Volcano vaporizer produced comparable or slightly higher THC plasma concentrations than smoking. Measured CO in exhaled vapor sessions diminished very slightly, while it increased after smoking ($p<0.001$). Self-reported visual analogue scales of the associated high were virtually identical in vaporization vs. smoking sessions and increased with higher potency material. A contention was advanced that the absence of CO increase after vaporization can be equated to "little or no exposure to gaseous combustion toxins." Given that no measures of PAH or other components were undertaken, the assertion is questionable. It was also stated that there were no reported adverse events. Some 12 subjects preferred the Volcano, 2 chose smoking, and 2 had no preference as to technique, making the vaporizer "an acceptable system" and providing "a safer way to deliver THC."

A recent [202, 117] examined interactions of 3.2 % THC NIDA cannabis vaporized in the Volcano in conjunction with opioid treatment in a 5-day inpatient trial in 21 patients with chronic pain (Table 18.1). All subjects were prior cannabis smokers. Overall, pain scores were reduced from 39.6 to 29.1 on a VAS, a 27 % reduction, by day 5. Pain scores in subjects on morphine fell from 34.8 to 24.1, while in subjects taking oxycodone, scores dropped from 43.8 to 33.6.

The clinical studies performed with vaporizers to date have been very small pilot studies conducted over very limited timeframes (i.e., for a maximum of 5 days). Thus, these studies cannot contribute in any meaningful fashion toward possible FDA approval of vaporized cannabis as a delivery technique, device, or drug under existing policies dictated by the *Botanical Guidance* [32]. It is likewise quite unlikely that the current AE profile of smoked or vaporized cannabis would meet FDA requirements. The fact that all the vaporization trials to date have been undertaken only in cannabis-experienced subjects does not imply that results would generalize to larger patient populations. Moreover, there is certainly no reason to expect AE profiles to be better in cannabis-naïve patients. Additionally, existing standardization of cannabis product and delivery via vaporization seem far off the required marks. Although vaporizers represent an alternate delivery method devoid of the illegality associated with smoked cannabis, the presence of toxic ingredients such as PAH, ammonia, and acetaldehyde in cannabis vapor are unlikely to be acceptable to FDA in any significant amounts. Existing vaporizers still lack portability or convenience [28]. A large Internet survey revealed that only 2.2 % of cannabis users employed vaporization as their primary cannabis intake method [118]. While studies to date have established that lower temperature vaporization in the Volcano, but not necessarily other devices, can reduce the relative amounts of noxious by-products of combustion, it has yet to be demonstrated that they are totally eliminated. Until or unless this goal is achieved, along with

requisite benchmarks of herbal cannabis quality, safety, and efficacy in properly designed randomized clinical trials, vaporization remains an unproven technology for therapeutic cannabinoid administration.

Evidence for Cannabis-Based Medicines

Cannador is a cannabis extract in oral capsules, with differing THC:CBD ratios [51]. Cannador was utilized in a phase III RCT of spasticity in multiple sclerosis (CAMS) (Table 18.1) [119]. While no improvement was evident in the Ashworth Scale, reduction was seen in spasm-associated pain. Both THC and Cannador improved pain scores in follow-up [120]. Cannador was also employed for postherpetic neuralgia in 65 patients, but without success (Table 18.1) [121, 122]. Slight pain reduction was observed in 30 subjects with postoperative pain (CANPOP) not receiving opiates, but psychoactive side effects were notable (Table 18.1).

Sativex® is a whole-cannabis-based extract delivered as an oromucosal spray that combines a CB_1 and CB_2 partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids, and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring [51, 123]. It is approved in Canada for spasticity in MS and under a Notice of Compliance with Conditions for central neuropathic pain in multiple sclerosis and treatment of cancer pain unresponsive to opioids. Sativex is also approved in MS in the UK, Spain, and New Zealand, for spasticity in multiple sclerosis, with further approvals expected soon in some 22 countries around the world. Sativex is highly standardized and is formulated from two *Cannabis sativa* chemovars predominating in THC and CBD, respectively [124]. Each 100 µl pump-action oromucosal spray of Sativex yields 2.7 mg of THC and 2.5 mg of CBD plus additional components. Pharmacokinetic data are available [125–127]. Sativex effects begin within an interval allowing dose titration. A very favorable adverse event profile has been observed in the development program [27, 128]. Most patients stabilize at 8–10 sprays per day after 7–10 days, attaining symptomatic control without undue psychoactive sequelae. Sativex was added to optimized drug regimens in subjects with uncontrolled pain in every RCT (Table 18.1). 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. One phase IIB dose-ranging study has already been completed [201]. Available clinical trials with Sativex have been independently assessed [129, 130].

In a phase II study of 20 patients with neurogenic symptoms [131], significant improvement was seen with both Tetranabinex (high-THC extract without CBD) and Sativex on pain, with Sativex displaying better symptom control ($p<0.0001$), with less intoxication (Table 18.1).

In a phase II study of intractable chronic pain in 24 patients [132], Sativex again produced the best results compared to Tetranabinex ($p<0.001$), especially in MS ($p<0.0042$) (Table 18.1).

In a phase III study of brachial plexus avulsion ($N=48$) [133], pain reduction with Tetranabinex and Sativex was about equal (Table 18.1).

In an RCT of 66 MS subjects, mean Numerical Rating Scale (NRS) analgesia favored Sativex over placebo (Table 18.1) [134].

In a phase III trial ($N=125$) of peripheral neuropathic pain with allodynia [135], Sativex notably alleviated pain levels and dynamic and punctate allodynia (Table 18.1).

In a safety-extension study in 160 subjects with various symptoms of MS [136], 137 patients showed sustained improvements over a year or more in pain and other symptoms [99] without development of any tolerance requiring dose escalation or withdrawal effects in those who voluntarily discontinued treatment suddenly. Analgesia was quickly reestablished upon Sativex resumption.

In a phase II RCT in 56 rheumatoid arthritis sufferers over 5 weeks with Sativex [137], medicine was limited to only 6 evening sprays (16.2 mg THC + 15 mg CBD). By study end, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain all favored Sativex (Table 18.1).

In a phase III RCT in intractable cancer pain on opioids ($N=177$), Sativex, Tetranabinex THC-predominant extract, and placebo were compared [138] demonstrating strongly statistically significant improvements in analgesia for Sativex only (Table 18.1). This suggests that the CBD component in Sativex was necessary for benefit.

In a 2-week study of spinal cord injury pain, NRS of pain was not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were positive (Table 18.1). Additionally, an RCT of intractable lower urinary tract symptoms in MS also demonstrated pain reduction (Table 18.1).

The open-label study of various polyneuropathy patients included Sativex patients with 3 obtaining 21.56 % mean pain relief after 3 months (2/3 > 30 %), and 4 achieving 27.6 % relief after 6 months (2/4 > 30 %), comparable to conventional agents [80].

A recently completed RCT of Sativex in intractable cancer pain unresponsive to opioids over 5 weeks was performed in 360 subjects (Table 18.1). Results of a Continuous Response Analysis (CRA) showed improvements over placebo in the low-dose ($p=0.08$) and middle-dose cohorts ($p=0.038$) or combined ($p=0.006$). Pain NRS improved over placebo in the low-dose ($p=0.006$) and combined cohorts ($p=0.019$).

Sleep has improved markedly in almost all Sativex RCTs in chronic pain based on symptom reduction, not a hypnotic effect [139].

The adverse event (AE) profile of Sativex has been quite benign with bad taste, oral stinging, dry mouth, dizziness, nausea, or fatigue most common, but not usually prompting discontinuation [128]. Most psychoactive sequelae are early and transient and have been notably lowered by more recent application of a slower, less aggressive titration schedule. While no direct comparative studies have been performed with Sativex and other agents, AE rates were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher, likely due to the presence of accompanying CBD [28, 51]. Similarly, Sativex displayed a superior AE profile compared to smoked cannabis based on safety-extension studies of Sativex [28, 99], as compared to chronic use of cannabis with standardized government-supplied material in Canada for chronic pain [140] and the Netherlands for various indications [141, 142] over a period of several months or more. All AEs are more frequent with smoked cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex [27, 28, 128]. A recent meta-analysis suggested that serious AEs associated with cannabinoid-based medications did not differ from placebo and thus could not be attributable to cannabinoid use, further reinforcing the low toxicity associated with activation of cannabinoid systems.

Cannabinoid Pitfalls: Are They Surmountable?

The dangers of COX-1 and COX-2 inhibition by nonsteroidal anti-inflammatory drugs (NSAIDS) of various design (e.g., gastrointestinal ulceration and bleeding vs. coronary and cerebrovascular accidents, respectively) [143, 144] are unlikely to be mimicked by either THC or CBD, which produce no such activity at therapeutic dosages [49].

Natural cannabinoids require polar solvents and may be associated with delayed and sometimes erratic absorption after oral administration. Smoking of cannabis invariably produces rapid spikes in serum THC levels; cannabis smoking attains peak levels of serum THC above 140 ng/ml [145, 146], which, while desirable to the recreational user, has no necessity or advantage for treatment of chronic pain [28]. In contrast, comparable amounts of THC derived from oromucosal Sativex remained below 2 ng/ml with much lower propensity toward psychoactive sequelae [28, 125], with subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 [100]. It is clear from RCTs that such psychoactivity is not a necessary accompaniment to pain control. In contrast, intoxication has continued to be prominent with oral THC [73].

In comparison to the questionable clinical trial blinding with smoked and vaporized cannabis discussed above, all indications are that such study blinding has been demonstrably effective with Sativex [147, 148] by utilizing a placebo spray with identical taste and color. Some 50 % of Sativex subjects in RCTs have had prior cannabis exposure, but results of two studies suggest that both groups exhibited comparable results in both treatment efficacy and side effect profile [134, 135].

Controversy continues to swirl around the issue of the potential dangers of cannabis use medicinally, particularly its drug abuse liability (DAL). Cannabis and cannabinoids are currently DEA schedule I substances and are forbidden in the USA (save for Marinol in schedule III and nabilone in schedule II) [73]. This is noteworthy in itself because the very same chemical compound, THC, appears simultaneously in schedule I (as THC), schedule II (as nabilone), and schedule III (as Marinol). DAL is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal, and dependency plus the drug's overall observed rates of abuse and diversion. Drugs that are smoked or injected are commonly rated as more reinforcing due to more rapid delivery to the brain [149]. Sativex has intermediate onset. It is claimed that CBD in Sativex reduces the psychoactivity of THC [28]. RCT AE profiles do not indicate euphoria or other possible reinforcing psychoactive indicia as common problems with its use [99]. Similarly, acute THC effects such as tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, and intraocular pressure decreases undergo prominent tachyphylaxis with regular usage [150]. Despite that observation, Sativex has not demonstrated dose tolerance to its therapeutic benefits on prolonged administration, and efficacy has been maintained for up to several years in pain conditions [99].

The existence or severity of a cannabis withdrawal syndrome remains under debate [151, 152]. In contrast to reported withdrawal sequelae in recreational users [153], 24 subjects with MS who volunteered to discontinue Sativex after a year or more suffered no withdrawal symptoms meeting Budney criteria. While symptoms such as pain recurred after some 7–10 days without Sativex, symptom control was rapidly reattained upon resumption [99].

Finally, no known abuse or diversion incidents have been reported with Sativex to date (March 2011). Formal DAL studies of Sativex vs. Marinol and placebo have been completed and demonstrate lower scores on drug liking and similar measures at comparable doses [155].

Cognitive effects of cannabis also remain at issue [155, 156], but less data are available in therapeutic applications. Studies of Sativex in neuropathic pain with allodynia have revealed no changes vs. placebo on Sativex in portions of the Halstead-Reitan Battery [135], or in central neuropathic pain in MS [134], where 80 % of tests showed no significant differences. In a recent RCT of Sativex vs. placebo in MS patients, no cognitive differences of note were observed

[157]. Similarly, chronic Sativex use has not produced observable mood disorders.

Controversies have also arisen regarding the possible association of cannabis abuse and onset of psychosis [156]. However, an etiological relationship is not supported by epidemiological data [158–161], but may well be affected by dose levels and duration, if pertinent. One may speculate that lower serum levels of Sativex combined with antipsychotic properties of CBD [52, 162, 163] might attenuate such concerns. Few cases of related symptoms have been reported in SAFEX studies of Sativex.

Immune function becomes impaired in experimental animals at cannabinoid doses 50–100 times necessary to produce psychoactive effects [164]. In four patients smoking cannabis medicinally for more than 20 years, no changes were evident in leukocyte, CD4, or CD8 cell counts [155]. MS patients on Cannador demonstrated no immune changes of note [165] nor were changes evident in subjects smoking cannabis in a brief trial in HIV patients [166]. Sativex RCTs have demonstrated no hematological or immune dysfunction.

No effects of THC extract, CBD extract, or Sativex were evident on the hepatic cytochrome P450 complex [167] or on human CYP450 [168]. Similarly, while Sativex might be expected to have additive sedative effects with other drugs or alcohol, no significant drug-drug interactions of any type have been observed in the entire development program to date.

No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/ml of THC [169]. Four oromucosal sprays of Sativex (exceeding the average single dose employed in therapy) produced serum levels well below this threshold [28]. As with other cannabinoids in therapy, it is recommended that patients not drive nor use dangerous equipment until accustomed to the effects of the drug.

Future Directions: An Array of Biosynthetic and Phytocannabinoid Analgesics

Inhibition of Endocannabinoid Transport and Degradation: A Solution?

It is essential that any cannabinoid analgesic strike a compromise between therapeutic and adverse effects that may both be mediated via CB_1 mechanisms [34]. Mechanisms to avoid psychoactive sequelae could include peripherally active synthetic cannabinoids that do not cross the blood-brain barrier or drugs that boost AEA levels by inhibiting fatty-acid amide hydrolase (FAAH) [170] or that of 2-AG by inhibiting monoacylycerol lipase (MGL). CBD also has this effect [50] and certainly seems to increase the therapeutic index of THC [51].

In preclinical studies, drugs inhibiting endocannabinoid hydrolysis [171, 172] and peripherally acting agonists [173] all show promise for suppressing neuropathic pain. AZ11713908, a peripherally restricted mixed cannabinoid agonist, reduces mechanical allodynia with efficacy comparable to the brain penetrant mixed cannabinoid agonist WIN55,212-2 [173]. An irreversible inhibitor of the 2-AG hydrolyzing enzyme MGL suppresses nerve injury-induced mechanical allodynia through a CB_1 mechanism, although these anti-allodynic effects undergo tolerance following repeated administration [172]. URB937, a brain impermeant inhibitor of FAAH, has recently been shown to elevate anandamide outside the brain and suppress neuropathic and inflammatory pain behavior without producing tolerance or unwanted CNS side effects [171]. These observations raise the possibility that peripherally restricted endocannabinoid modulators may show therapeutic potential as analgesics with limited side-effect profiles.

The Phytocannabinoid and Terpenoid Pipeline

Additional phytocannabinoids show promise in treatment of chronic pain [123, 163, 174]. Cannabichromene (CBC), another prominent phytocannabinoid, also displays anti-inflammatory [175] and analgesic properties, though less potently than THC [176]. CBC, like CBD, is a weak inhibitor of AEA reuptake [177]. CBC is additionally a potent TRPA1 agonist [178]. Cannabigerol (CBG), another phytocannabinoid, displays weak binding at both CB_1 and CB_2 [179, 180] but is a more potent GABA reuptake inhibitor than either THC or CBD [181]. CBG is a stronger analgesic, anti-erythema, and lipooxygenase agent than THC [182]. CBG likewise inhibits AEA uptake and is a TRPV1 agonist [177], a TRPA1 agonist, and a TRPM8 antagonist [178]. CBG is also a phospholipase A2 modulator that reduces PGE-2 release in synovial cells [183]. Tetrahydrocannabivarin, a phytocannabinoid present in southern African strains, displays weak CB_1 antagonism [184] and a variety of anticonvulsant activities [185] that might prove useful in chronic neuropathic pain treatment. THCV also reduced inflammation and attendant pain in mouse experiments [187]. Most North American [187] and European [188, 189] cannabis strains have been bred to favor THC over a virtual absence of other phytocannabinoid components, but the latter are currently available in abundance via selective breeding [124, 190].

Aromatic terpenoid components of cannabis also demonstrate pain reducing activity [123, 163]. Myrcene displays an opioid-type analgesic effect blocked by naloxone [191] and reduces inflammation via PGE-2 [192]. β-Caryophyllene displays anti-inflammatory activity on par with phenylbutazone via PGE-1 [193], but contrasts by displaying gastric cytoprotective activity [194]. Surprisingly, β-caryophyllene has proven to be a phytocannabinoid in its own right as a selective CB_2 agonist [195]. α-Pinene inhibits PGE-1 [196], and linalool acts as a local anesthetic [197].

Summary

Basic science and clinical trials support the theoretical and practical basis of cannabinoid agents as analgesics for chronic pain. Their unique pharmacological profiles with multimodality effects and generally favorable efficacy and safety profiles render cannabinoid-based medicines promising agents for adjunctive treatment, particularly for neuropathic pain. It is our expectation that the coming years will mark the advent of numerous approved cannabinoids with varying mechanisms of action and delivery techniques that should offer the clinician useful new tools for treating pain.

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Study Finds Cannabis Compounds Prevent Infection By Covid-19 Virus

FORBES
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Compounds in cannabis can prevent infection from the virus that causes Covid-19 by blocking its entry into cells, according to a study published this week by researchers affiliated with Oregon State University. A report on the research, "Cannabinoids Block Cellular Entry of SARS-CoV-2 and the Emerging Variants," was published online on Monday by the *Journal of Natural Products*.

The researchers found that two cannabinoid acids commonly found in hemp varietals of cannabis, cannabigerolic acid, or CBGA, and cannabidiolic acid, also known as CBDA, can bind to the spike protein of SARS-CoV-2, the virus that causes Covid-19. By binding to the spike protein, the compounds can prevent the virus from entering cells and causing infection, potentially offering new avenues to prevent and treat the disease.

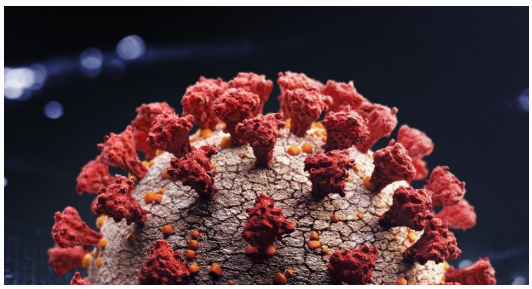
"Orally bioavailable and with a long history of safe human use, these cannabinoids, isolated or in hemp extracts, have the potential to prevent as well as treat infection by SARS-CoV-2," the researchers wrote in an abstract of the study.

The study was led by Richard van Breemen, a researcher with Oregon State's Global Hemp Innovation Center in the College of Pharmacy and Linus Pauling Institute, in collaboration with scientists at the Oregon Health & Science University. Van Breeman said that the cannabinoids studied are common and readily available.

“These cannabinoid acids are abundant in hemp and in many hemp extracts,” van Breemen said, as quoted by local media. “They are not controlled substances like THC, the psychoactive ingredient in marijuana, and have a good safety profile in humans.”

Cannabinoids Effective Against New Variants

Van Breemen added that CBDA and CBGA blocked the action of emerging variants of the virus that causes Covid-19, saying that “our research showed the hemp compounds were equally effective against variants of SARS-CoV-2, including variant B.1.1.7, which was first detected in the United Kingdom, and variant B.1.351, first detected in South Africa.”



The spike protein is the same part of the virus target by Covid-19 vaccines and antibody therapies. In addition to the spike protein, SARS-CoV-2 has three more structural proteins as well as 16 nonstructural proteins and several compounds van Breemen characterized as “accessory” proteins, all of which are potential targets for drugs developed to prevent Covid-19.

“Any part of the infection and replication cycle is a potential target for antiviral intervention, and the connection of the spike protein’s receptor binding domain to the human cell surface receptor ACE2 is a critical step in that cycle,” van Breeman said. “That means cell entry inhibitors, like the acids from hemp, could be used to prevent SARS-CoV-2 infection and also to shorten infections by preventing virus particles from infecting human cells. They bind to the spike proteins so those proteins can’t bind to the

ACE2 enzyme, which is abundant on the outer membrane of endothelial cells in the lungs and other organs."

Although further research is needed, van Breemen noted that study shows the cannabinoids could be developed into drugs to prevent or treat Covid-19.

"These compounds can be taken orally and have a long history of safe use in humans," van Breemen noted. "They have the potential to prevent as well as treat infection by SARS-CoV-2. CBDA and CBGA are produced by the hemp plant as precursors to CBD and CBG, which are familiar to many consumers. However, they are different from the acids and are not contained in hemp products."

Van Breeman also noted that the research showed the cannabinoids were effective against new variants of the virus, which he said are "one of the primary concerns" in the pandemic for health officials and clinicians.

"These variants are well known for evading antibodies against early lineage SARS-CoV-2, which is obviously concerning given that current vaccination strategies rely on the early lineage spike protein as an antigen," said van Breemen. "Our data show CBDA and CBGA are effective against the two variants we looked at, and we hope that trend will extend to other existing and future variants."

The researcher added that "resistant variants could still arise amid widespread use of cannabinoids but that the combination of vaccination and CBDA/CBGA treatment should make for a much more challenging environment for SARS-CoV-2."