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Cannabis and Pain: A Clinical Review

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Abstract

Introduction: Cannabis has been used for medical purposes across the world for centuries. As states and countries implement medical and recreational cannabis policies, increasing numbers of people are using cannabis pharmacotherapy for pain. There is a theoretical rationale for cannabis' efficacy for pain management, although the subjective pain relief from cannabis may not match objective measurements of analgesia. As more patients turn to cannabis for pain relief, there is a need for additional scientific evidence to evaluate this increase.

Materials and Methods: Research for this review was performed in the PubMed/National Library of Medicine database.

Discussion: Preclinical studies demonstrate a narrow therapeutic window for cannabis as pharmacotherapy for pain; the body of clinical evidence for this indication is not as extensive. A recent meta-analysis of clinical trials of cannabis and cannabinoids for pain found modest evidence supporting the use of cannabinoid pharmacotherapy for pain. Recent epidemiological studies have provided initial evidence for a possible reduction in opioid pharmacotherapy for pain as a result of increased implementation of medical cannabis regimens.

Conclusion: With increased use of medical cannabis as pharmacotherapy for pain comes a need for comprehensive risk-benefit discussions that take into account cannabis' significant possible side effects. As cannabis use increases in the context of medical and recreational cannabis policies, additional research to support or refute the current evidence base is essential to attempt to answer the questions that so many healthcare professionals and patients are asking.

Keywords: anandamide; cannabidiol; cannabinoids; endocannabinoid; pain; THC

Introduction: Promising Compounds, Changing Landscape

Cannabis has been used around the world for centuries and the purpose for its use has varied throughout that time.[1] However, the utilization of cannabis for medicinal purposes has been consistent. Starting with the Chinese around 2900 B.C., many civilizations have transcribed their use of cannabis for a variety of conditions, from joint pain and muscle spasms to conditions such as gout and malaria.[1] While cannabis has been deployed medicinally for myriad medical conditions, the scientific rationale for its efficacy for these conditions is, in many cases, not clear. Four thousand years later, scientists are still trying to determine the exact medical conditions, if any, cannabis is effective in treating.

Research into cannabis and its uses has been hindered by a debate over its legality.[2] In 1976, the United States Controlled Substances Act classified cannabis as a Schedule I drug, meaning that it has a high potential for abuse and no accepted medical uses. However, as of March 2017, 28 states and the District of Columbia have enacted laws allowing the medical use of cannabis and 8 states, plus the District of Columbia, have legalized recreational use of cannabis.[3] The accepted

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conditions vary from state to state, in large part, due to the lack of randomized placebo-controlled studies researching the efficacy of cannabis for specific ailments.[4] Despite a paucity of standardized and controlled trial research to evaluate the short- and long-term health outcomes of cannabis use, all states are consistent in including chronic pain as one of the conditions for which cannabis is an approved pharmacotherapy. Indeed, pain relief is the most commonly cited reason for the medical use of cannabis.[4–6]

Whether cannabis is the best treatment for pain or not, many patients around the world believe that cannabis has helped them with their pain.[7] As more and more states legalize cannabis for medicinal uses, a greater number of patients will ask their healthcare provider if it would be an effective treatment for their condition. Healthcare providers are in a difficult situation: there are only two cannabinoids currently approved by the United States Food and Drug Administration, and state regulations require them to recommend cannabis broadly, leaving the details about cannabis strains and dosing to be determined at the dispensaries. Interest in the use of cannabis for pain may be further catalyzed by a recent report put forth by the National Academies Committee on the Health Effects of Marijuana,[8] in which the authors concluded that there is "conclusive or substantial evidence" that cannabis is effective for the treatment of chronic pain in adults. Furthermore, even if physicians do not recommend cannabis for their own patients, they should at least be educated regarding the extensive effects of cannabis. Unfortunately, many patients currently use cannabis to treat a host of medical problems and do so without contacting their healthcare provider.[7] Healthcare professionals need to be prepared to answer questions regarding cannabis use and the potential effect it would have on each patient's treatment.

Cannabis and pain: a brief history

The utilization of cannabis for pain can be traced back to ancient Chinese texts, dating to 2900 B.C. The Shennong Ben Cao Jing, a Chinese encyclopedia on agriculture and medicine, contains the oldest written record of cannabis as a medicine, recommending cannabis for constipation, rheumatic pain, female reproductive tract disorders, and malaria.[9] Furthermore, the plant was used in conjunction with wine to anesthetize patients during surgical procedures.[10] The Chinese mostly utilized cannabis seeds that contain very low levels of delta-9-tetrahydrocannabinol (Δ^9THC), one of the main compounds in cannabis thought to have therapeutic effects.[10]

Around 1000 year B.C., more parts of the cannabis plant started to be used medicinally in India. The female plant's flowers were utilized and three different preparations of cannabis with varying degrees of potency were developed.[9] The strongest preparations were used as an analgesic, hypnotic, tranquilizer, antispasmodic, and anti-inflammatory agent.[11,12] It was not until the early 19th century that cannabis started to be explored in Western medicine.[13]

Although the use of cannabis as a medicine in western cultures started off slowly, by the end of the 19th century, over 100 publications on medicinal cannabis were published in Europe and the United States.[14] Within that time, the medical indications for cannabis mostly focused on its hypnotic and analgesic effects. Since then, medical cannabis use has waxed and waned due to legal restrictions as well as the difficulty with replicating its effects between individuals.[11,15] Since the 1960s, both recreational cannabis use and medicinal cannabis use have increased rapidly in the United States. In 2015, an estimated 22.2 million Americans aged 12 or older were current users of cannabis, which corresponds to 8.3% of the U.S. population aged 12 or older.[16] Recently, research into cannabis expanded exponentially and the use of cannabis for pain became one of the most widely studied subtopics.[17]

There are two ways to consider the rationale for cannabis pharmacotherapy for pain, conceptually and according to the evidence base. In this review, we will examine both.

Materials and Methods

Standard searches of the PubMed/National Library of Medicine database for the listed keywords and references from literature for pertinence to cannabis and the clinical management of pain were undertaken.

The subjective experience of pain

Pain has long been characterized as a subjective experience encompassing sensory-physiological, motivational-affective, and cognitive-evaluative components.[18] Approximately, 100 million U.S. adults are encumbered by chronic pain[19,20]; pain motivates greater than 50% of all annual physician visits,[21] and recent estimates indicate a pain-related financial burden in excess of $600 billion in annual healthcare costs and lost productivity.[19] The three main pain systems are nociceptive, neuropathic, and central.[22] Nociceptive pain is caused by damage to body tissue and is usually described as sharp, aching, or throbbing pain. In response to tissue injury, invading immune cells secrete histamine, serotonin,

bradykinin, prostaglandin, elevated levels of tumor necrosis factor alpha, interleukin 1 beta, interleukin 6, and interleukin 17.[23] Signals of tissue injury are carried by fine C- and A-gamma peripheral nerves to dorsal root ganglia, up the spinothalamic track to the thalamus, and then on to the cortical area.[24] It is important to note that this is the only nociceptive system by which the survival value of pain to alert the organism to potential or occurring tissue damage exists. Nociceptive pain has warning and defensive properties. The other two pain systems, neuropathic and central, involve nonfunctional pain signals with disease involving the interpreting system.[25,26]

Neuropathic pain is caused by damage to sensory or spinal nerves, which send inaccurate pain messages to higher centers.[26] For example, in diabetic neuropathy, the origin of foot pain is not in the tissue, but rather, the peripheral nerves. The disease attacks the peripheral nerves, resulting in an aberrant signal interpreted by the brain as pain in the feet. Centralized pain is the result of amplification of peripheral signals due to persistent central nervous system dysfunction.[22] Pain may be present despite a lack of a clear peripheral cause. A classic example is fibromyalgia.[25] The Clauw metaphor is that the electric guitar is a quiet instrument until the amplifier (brain) is plugged in. The central nervous system amplification makes the pain impossible to ignore.

The complex nature of pain can make it difficult to understand another's pain. First, there are many genetic variants of pain, such as alleles of the SCN9A gene. SCN9A variants determine typical pain experiences, heightened pain, and rarely, the inability to feel pain by regulating the expression of voltage-gated sodium channel Na(v)1.7 mRNA, a resulting protein that is an important contributor to generation and conduction of action potentials of nociceptive neurons of dorsal root ganglia.[24] Low Na(v)1.7 results in low initiation and propagation of pain signals, and therefore high pain thresholds while high Na(v)1.7 would result in exaggerated pain sensitivity.

Second, the relationship of the observer to the pain experiencer is relevant to the observer's ability to gauge the extent of the experiencer's pain. When one feels close to another, one is more concerned with another's pain, in part, because different brain areas are activated by empathic connection versus when considering the pain experience of a stranger.[27] For example, emergency physicians were thrice more likely to prescribe opioids to patients in motor vehicle accidents who had not completed high school than patients who shared their graduate level of education, suggesting that empathy and concern about prescribing a drug with addictive potential may affect the decision.[28]

Finally, pain is an affect, or a subjective aspect of an emotion. However, an affect is a combination of innate endowment, childhood and adult history as metabolized through the consciousness of the person, and interpersonal relatedness. Pain experienced by a person with the normal SCN9A gene endowment might be dramatically different from pain caused by the same peripheral injury in someone with the high pain SCN9A gene variant suffering from serious psychiatric disorders such as major depressive disorder or borderline personality disorder.[29,30] These individuals' responses to pain will likely be different.

Substances Used for Pain

Cannabis is rarely the first drug that a patient takes to mitigate pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit pain by addressing local tissue inflammation. They inhibit cyclooxygenase (COX), an enzyme required to make the vasodilator prostaglandin. Therefore, the painful swelling of peripheral tissues is decreased. NSAIDs can be used daily for prolonged periods to manage inflammatory conditions such as arthritis.[31]

Alcohol also has an extensive history as a substance used in response to pain, and epidemiological data substantiate a high co-occurrence of pain and alcohol use.[32] For example, past-month pain is highly prevalent among individuals seeking treatment for alcohol use disorder (AUD; e.g., 73%),[33] and chronic pain patients are up to 60% more likely to endorse heavy drinking and/or meet diagnostic criteria for AUD, even after accounting for concurrent psychopathology and other substance use problems.[34–36] Although there is some evidence that drinking alcohol can confer short-term pain inhibition, such effects may require consumption at doses that exceed guidelines for moderate daily use, and the development of tolerance would likely require more alcohol to achieve the same degree of acute analgesia.[37] There is also converging evidence[38] that periods of abstinence following chronic alcohol consumption tend to be associated with increased sensitivity to pain, which in turn could promote relapse to drinking. Alcohol is mood-altering and addictive, thus physicians do not recommend that patients use alcohol to treat either acute or chronic pain.

Like alcohol, nicotine and tobacco smoking have long been implicated in the amelioration of pain.[39,40] Prevalence estimates indicate that individuals with chronic pain (vs. no chronic pain) are about twice as likely to be current smokers, with rates of smoking among

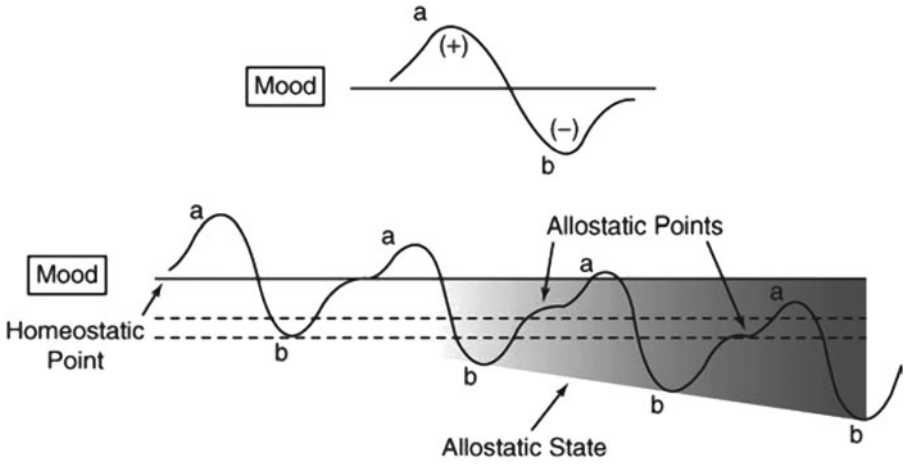

FIG. 1. Opponent process theory.

treatment-seeking pain patients ranging from 49% to 68%.[41–44] Although a recent meta-analysis showed that nicotine can produce modest acute analgesia among humans, chronic cigarette smoking has been identified as a unique risk factor in the incidence and progression of several chronically painful conditions.[45,46] In terms of using nicotine for pain relief, the experience of pain has been shown to be a potent motivator of smoking behavior,[47] and pain patients have reliably endorsed smoking cigarettes to cope with pain.[48] Commensurate with evidence of complex interrelations between pain and tobacco smoking, research has also shown that daily smokers are nearly five times more likely to meet past-year diagnostic criteria for opioid abuse or dependence than never smokers.[49]

The aberrant use of opioid medications is a growing public health crisis, and factors that have been shown to confer heightened risk for prescription opioid misuse include the presence of chronic pain and co-occurring substance use and mood disorders.[50–52] Opioid use accelerated in recent decades as a result of a social movement that cited cultural, societal, religious, and political attitudes as reasons for inadequate pain management.[53] The result of the widespread increase in opioid prescribing in the United States was quadrupling of opioid-caused deaths over 15 years.[54] One out of every 32 patients prescribed at least 200 morphine milligram equivalents per day died from chronic pain treatment.[55]

As with other short-acting, consciousness-altering drugs, opioids are regarded by many patients as the best pharmacotherapy for pain relief. However, despite beliefs to the contrary, opioids are not optimal pharmacotherapy for chronic pain. Koob and LeMoal's opponent process theory is one way to understand this phenomenon.[56] Every dose of opioids helps pain, the "a" process. Over time, drivers of dysphoria: pain, anxiety, and depression, the "b" process, overshoot the amelioration of pain (Fig. 1) Consistent with opponent process theory and emerging research on pain and substance use, an evolving allostatic load conceptualization of pain and addiction posits that chronic substance use (along with commensurate repeated opponent process cycles of substance-induced analgesia and withdrawal-induced hyperalgesia) can dysregulate overlapping neural substrates and homeostatic pain mechanisms to engender a persistent imbalance that favors pain facilitation.[57]

Gradually, opioid-induced hyperalgesia is induced. This is a state where pain increases and generalizes due to central sensitization. In response to this pain, prescribed or illegally obtained doses of opioids are increased in an attempt to override the pain system.

Cannabis is now being considered in the same way that opioids were decades ago, the combination of a drug class that is experienced as pain-relieving medications in the context of a social movement supporting the treatment for pain. We now move to an examination of the mechanisms of cannabis effects on pain and the limited number of studies available that examine the outcomes of pain treatment with cannabis.

The endocannabinoid system and mechanisms of pain reduction

Neural and nonneural cells in injured tissues produce arachidonic acid derivatives called endocannabinoids.[58]

They modulate neural conduction of pain signals by mitigating sensitization and inflammation through the activation of cannabinoid receptors that are also targeted by Δ^9THC.[59] CB_1 receptors modulate neurotransmitter release in the brain and spinal cord.[60] CB_1 receptors are also present in nociceptive and nonnociceptive sensory neurons of the dorsal root ganglion and trigeminal ganglion,[61] as well as in defense cells such as macrophages, mast cells, and epidermal keratinocytes.[62] CB_2 receptors are expressed at considerable levels in cells of hematopoietic origin.[63] Few CB_2 receptors are located in the brain, spinal cord, and dorsal root ganglion, but they increase in response to peripheral nerve damage.[64] They regulate neuroimmune interactions and interfere with inflammatory hyperalgesia.

Endocannabinoids, anandamide, and 2-arachidonoyl-*sn*-glycerol (2-AG) are produced in injured tissues through distinct biochemical pathways to suppress sensitization and inflammation by activation of cannabinoid (CB) receptors. Anandamide can act as an autocrine or paracrine messenger and follows one of two pathways. In a reaction catalyzed by fatty acid amide hydrolase, it can be broken down to arachidonic acid and ethanolamine or,[65] alternatively, it can be directly transformed by COX-2 into proalgesic prostamides.[66] Anandamide mobilizes in response to inflammation and nerve injury and modulates nociceptive signals by activating local CB_1 receptors. 2-AG is formed by the hydrolysis of phosphatidylinositol-4,5-biphosphate, a phospholipid at the center of a lipid pathway that produces numerous intracellular and transcellular messengers.[65] It plays a prominent role in the descending modulation of pain during acute stress.[67] Anandamide and 2-AG are recruited during tissue injury to provide a first response to nociceptive signals. Thus, understanding the function of endogenous cannabinoids helps explain the efficacy of exogenous cannabinoids, such as those found in the cannabis plant, in treating pain.

Therefore, the biologically hypothesized rationale for cannabinoid administration is whole-body exposure to exogenous cannabinoids to turn on pain inhibition. Of note, long-term studies of analgesia with exogenous cannabinoids would be necessary to adjudicate the question of whether pain could be continually suppressed in this manner, or whether the same hyperalgesic response to cannabinoids that is currently observed with opioids would ensue, another opponent process. Thus, physicians must be careful, just as with alcohol, nicotine, and opioids, about endorsing a drug where every use gives a subjective experience that pain is improved, and yet use of the drug over time has both hyperalgesic and potentially addictive properties.

Cannabis and pain studies

Results from studies evaluating cannabis pharmacotherapy for pain demonstrate the complex effects of cannabis-related analgesia. There are multiple randomized, controlled clinical trials that show cannabis as an effective pharmacotherapy for pain.[68] However, further examination of pre-clinical studies of cannabis in pain models underscores the nuances of cannabis' analgesic effects. THC has been shown to produce analgesic and antihyperalgesic effects in animal models,[69,70] and experimental research examining the effects of cannabis on human pain responding has focused either on healthy adults or clinical pain samples. For example, Wallace et al. tested the effects of smoked cannabis (low, medium, or high doses vs. inactive placebo) on intradermal capsaicin-induced pain responses using a randomized, double-blind, crossover trial in 15 healthy volunteers (mean age of 28.9; 58% male).[71] Results indicated a significant decrease in pain with the medium cannabis dose and a significant increase in pain with the high dose. No differences were observed with the low cannabis dose, and there was no effect on the area of hyperalgesia at any dose. The authors concluded that there is likely a therapeutic window of modest analgesia for smoked cannabis.

Another experimental study with 18 healthy female volunteers tested the effects of orally administered cannabis extract (vs. active placebo) on sunburn and intradermal capsaicin pain responses using a double-blind, crossover trial.[72] Results indicated that the cannabis extract did not produce any analgesic or antihyperalgesic effects. There was also some evidence of an unexpected hyperalgesic state in the cannabis group. These authors concluded that the utility of cannabis use for acute pain relief is limited by the poorly understood therapeutic window and the dose-dependent occurrence of psychotropic side effects.

In terms of clinical pain, a recent systematic review and meta-analysis of cannabinoids for medical use that examined 28 randomized trials among 2454 patients with chronic pain indicated that, compared with placebo, cannabinoids were associated with greater a reduction in pain (37% vs. 31%; OR 1.41, 95% CI 0.99 to 2.00) and greater average reduction in numerical pain ratings (–0.46, 95% CI –0.80 to –0.11).[73] Whiting et al. concluded that there was moderate evidence to support the use of cannabinoids for the treatment of chronic pain. In this review,

neuropathy was the most commonly cited source of chronic pain. The majority of studies focused on testing the effects of plant-derived cannabinoids. Only 5 of the 28 trials assessed the effects of vaporized or smoked cannabis plant flower. Of note, cannabinoids were associated with an increased risk for short-term adverse events, including serious adverse events, compared to placebo.

One recent study not included in Whiting's meta-analysis was a placebo-controlled trial of inhaled aerosolized cannabis, which demonstrated a dose-dependent reduction in diabetic peripheral neuropathy spontaneous pain ratings among patients with treatment-refractory pain.[74] Finally, and most recently, Wilsey et al. conducted a randomized, placebo-controlled crossover trial utilizing vaporized cannabis among 42 participants with central neuropathic pain related to spinal cord injury and disease.[75] Results indicated that vaporized cannabis flower reduced neuropathic pain scale ratings, but there was no evidence of a dose-dependent effect. These authors concluded that additional research is needed to examine how interactions among cannabinoids may influence analgesic responding.

Collectively, this research indicates that although the results of experimental studies with healthy adults are mixed, there is converging evidence to support the notion that cannabis can produce acute pain-inhibitory effects among individuals with chronic pain. This observation is consistent with determinations made by authors of the recent National Academies report on cannabis that there is "conclusive or substantial evidence" of benefit from cannabis or cannabinoids for chronic pain. However, it is important to also highlight their statement that more research is needed to better understand the efficacy, dose–response effects, routes of administration, and side effect profiles for cannabis products that are commonly used in the United States.[8]

Clinical issues

According to the DSM 5 heuristic,[76] a diagnosis of cannabis use disorder (CUD) requires a pattern of cannabis use leading to clinically significant impairment or distress characterized by the presence of two or more of 11 prototypical symptoms within a 12-month period. These symptoms can be organized into three broad categories: (1) physical symptoms including craving, withdrawal, and tolerance, (2) use-induced psychosocial problems, and (3) increased drug-use and/or drug-seeking behavior. It has been estimated that one out of every 10 people who ever use cannabis will develop a CUD,[77–79] and nationally representative U.S. data indicate that consequences consistent with CUD are endorsed by ~30% of all current users.[80] The cannabis withdrawal syndrome typically results from abrupt cessation with a time course that may persist for ~14 days following discontinuation (similar to tobacco withdrawal).[81–83] Importantly, both acute intoxication and withdrawal frequently produce symptoms that feature prominently among those with chronic pain (i.e., mood disturbance and sleep problems).[82]

Consistent with previously published conceptualizations of interrelations between pain and substance use,[39,40,84] pain and cannabis use may be expected to interact in the manner of a positive feedback loop, resulting in greater pain and the development or maintenance of CUD. Negative affect would also be hypothesized to play a key mechanistic role, which is consistent with the identification of negative affect as a principal component in theoretical conceptualizations of pain processing and addiction motivation.[85,86] Over time, bidirectional relationships between pain and cannabis use may result in more severe functional impairment, greater pain-induced motivation to use cannabis, and increased negative affect and sensitivity to pain during periods of cannabis abstinence. Furthermore, expectations that abstaining from cannabis may exacerbate both pain and negative affect could serve as important barriers to cannabis cessation.

One important implication of this conceptualization is that individuals with chronic pain may develop unique CUD profiles that require specialized treatment. For example, chronic pain patients who engage in treatment for CUD may benefit from taking additional measures to manage their pain during the early stages of cannabis abstinence. Similarly, patients receiving pain treatment may benefit from interventions that aim to reduce the use of cannabis for pain-coping purposes. Finally, given that pain motivates more than half of all annual physician visits in the United States,[87] patients who present to primary care with co-occurring pain and cannabis use may benefit from an integrated treatment delivered within that setting. Additional research is needed to better understand the interplay of pain and cannabis use both over time and during the course of a cessation attempt. Clinicians may also consider the utility of sequential or integrated treatment for pain and CUD.

As cannabis is evaluated as pharmacotherapy and its use becomes more widespread, its significant side effects remain. Like other substances, there are potential adverse effects with acute and chronic use. Cognitive impairment can occur with both acute and chronic

use, and adverse cognitive effects may be one area where the effects of chronic cannabis use could be worse than chronic opioid use. Although the acute effects of cannabis use, on driving for example, have received increasing attention with the implementation of medical and recreational cannabis policies, the effects of chronic use are better described.[88] Regular cannabis use, especially while the brain is under development, is associated with an increased risk of anxiety, depression, and psychotic illness, and cannabis can worsen the courses of these disorders.[68] These associations are especially important given the common co-occurrence of chronic pain and psychiatric conditions.[89] The implementation of medical and recreational cannabis policies offer an opportunity to collect longitudinal data on the effects of cannabis use. As we continue to collect such data, cannabis pharmacotherapy for pain management must be based upon thorough risk-benefit discussions.

Cannabis and Opioid Interactions

As more states introduce medical and recreational cannabis policies, we continue to learn more about the relationship between cannabis and opioids. Many patients have described a decreased need for prescription opioids after starting medical cannabis regimens. Many substances with addictive properties utilize common neural pathways, providing a theoretical basis for such anecdotes. Recently, rigorous studies have begun to provide evidence for these anecdotes as well. Bachhuber et al. described that states with medical cannabis laws had significantly lower annual opioid overdose mortality rates compared to states without medical cannabis.[90] This finding may be the result of patients with chronic pain initiating pharmacotherapy with medical cannabis, thereby lowering the need for opioid pharmacotherapy. Less reliance on opioid pharmacotherapy may in turn lead to fewer fatal opioid overdoses. A recent examination of Medicare claims data also showed that the use of prescription pain medications, including opioids, was significantly reduced in states following the implementation of medical cannabis laws. Finally, another study demonstrated that the percentage of drivers testing positive for opioids after traffic fatalities was significantly reduced in states with medical cannabis laws compared to states without such laws.[91] Taken together, these studies provide initial support for medical cannabis being correlated with decreased opioid-induced mortality. Further studies are necessary to further elucidate the role of cannabis as a potentially safer alternative to opioids for pharmacological pain management.

Conclusions

This is a pivotal time in the history of cannabis and cannabinoid research. In the context of increasing debates on the merits of medical and recreational cannabis policies, we need a corresponding increase in cannabis research. Many advocates on either side of these debates appear content to promote their agendas without placing priority on funding and supporting research that would answer key questions about the safety of cannabis and its potential medical indications. The often contentious debate about the efficacy of cannabis pharmacotherapy for pain is an important example. There is evidence, although limited, to support the use of cannabis pharmacotherapy in certain clinical scenarios. For example, if a patient with chronic pain and their healthcare provider work together through first- and second-line treatment modalities without success, a trial of cannabis or a cannabinoid may be a reasonable next step. As cannabis use increases, additional research to support or refute the current evidence base is essential to attempt to answer the questions that so many healthcare professionals and patients are asking.

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Abbreviations Used

2-AG = 2-arachidonoyl-*sn*-glycerol
AUD = alcohol use disorder
COX = cyclooxygenase
CUD = cannabis use disorder
NSAID = nonsteroidal anti-inflammatory drugs
THC = tetrahydrocannabinol