Vol 6 | Issue 1 | Pages 283-289

Journal of Clinical Anesthesia and Pain Management

ISSN: 2578-658X

Review Article

DOI: 10.36959/377/370

Is Cannabis a Viable Treatment of Chronic Non-Cancer Pain? - A Mini Review

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Abstract

The practice of pain medicine today is faced with the ever-rising burden of the nation's opioid epidemic. There has been a strong push to redefine chronic pain treatments and to find analgesic alternatives that avoid the harmful risks of opioid use that lead to diversion, overdose and addiction. Cannabis has been suggested to be an efficacious and safer alternative or replacement for opioids, but a large gap remains between the reported opioid-sparing benefits of cannabis and scientific evidence from high-quality research. This is largely due to the national restrictions on cannabis and its status as a Schedule 1 substance with the Drug Enforcement Agency. Despite this, the public availability of cannabis and cannabinoid products has grown exponentially. With shifts in public sentiment in general and increased state-specific legalization, cannabis is increasingly seen as a plausible medication for the treatment of many chronic conditions - especially in the field of pain medicine. However, the question remains: is cannabis a viable treatment of chronic non-cancer pain? The purpose of this article is to review the emergence of our country's opioid crisis, the known analgesic effects of cannabinoids and the endocannabinoid system, the legality of cannabis by US jurisdiction, the evidence on the therapeutic uses of cannabis, and finally the comparative relative risks and benefits of cannabis versus opioid medications in the treatment of chronic pain.

Keywords

Cannabis, Chronic pain, Opioids, Review

Introduction

The practice of pain medicine today is faced with the ever-rising burden of the nation's opioid epidemic. There has been a strong push to redefine chronic pain treatments and to find analgesic alternatives that avoid the harmful risks of opioid use that lead to diversion, overdose, and addiction. Cannabis has been suggested to be an efficacious and safer alternative or replacement for opioids [1], but a large gap remains between the reported opioid-sparing benefits of cannabis and scientific evidence from high-quality research. This is largely due to the national restrictions on cannabis and its status as a Schedule 1 substance with the Drug Enforcement Agency [2]. Despite this, the public availability of cannabis and cannabinoid products has grown exponentially. With shifts in public sentiment in general and increased state-specific legalization, cannabis is increasingly seen as a plausible medication for the treatment of many chronic conditions - especially in the field of pain medicine [3]. However, the question remains: is cannabis a viable treatment of chronic non-cancer pain? The purpose of this article is to review the emergence of our country's opioid crisis, the known analgesic effects of cannabinoids and the endocannabinoid system, the legality of cannabis by US jurisdiction, the evidence on the therapeutic uses of cannabis, and finally the comparative relative risks and benefits of cannabis versus opioid medications in the treatment of chronic pain.

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Accepted: March 24, 2022

Published online: March 26, 2022

Citation: Estioko MDT, Khan H, Yim D, et al. (2022) Is Cannabis a Viable Treatment of Chronic Non-Cancer Pain? - A Mini Review. J Clin Anesth Pain Manag 6(1):283-289

Emergence of Our Country's Opioid Crisis

Understanding the historical origins of the current opioid epidemic is essential to understanding the current debate on alternative management strategies for chronic pain. The development of morphine and its use for Civil War soldiers in the mid-19th century, as well as the lack of many alternatives for their ongoing chronic pain, led to chronic prescribing of morphine and a related opioid epidemic of the 1870s and 1880s, when per capita consumption of opiates approximately tripled [4]. This in turn led to a change in sentiment in the medical community, who returned to favoring non-pharmacologic measures of pain management and even encouraging cancer patients to minimize use of opioids until they were in the terminal phase. Accompanying this change was an increasing criminalization and restriction of narcotic sales and use throughout the early decades of the 20th century, and an accompanying growing black market, particularly for heroin (diacetylmorphine).

The roots of the current epidemic began in the latter decades of the 20th century, when members of the medical community began to publish articles describing an under-reliance on opioid analgesics and an associated under-treatment of pain. This led to a liberalization of the use of opioids, not only for cancer pain, but also for other chronic non-cancer pain. This became more widespread, with the American Pain Society's "pain as the fifth vital sign" campaign in 1995, adopted by the Veteran's Health Administration in 1999, the Joint Commission's inclusion of standards for pain management in 2000, as well as increasing emphasis on pain control in graduate medical education. During the same period, pharmaceutical companies began receiving approvals for new formulations of opioid pills, such as extended-release oxycodone (OxyContin). From 1997 to 2002, OxyContin prescriptions increased from 670,000 to 6.2 million [5]. Overall, opioid prescriptions tripled starting in the 1990s and peaking around 2011, accompanied by increasing misuse of delayed or extended-release dosage forms (e.g., crushing and insufflating or injecting) and a wave of opioid overdose-related deaths [6].

Following close on this first epidemic wave of prescription opioids, by the mid-2000s, the number of heroin users began to increase, accompanied by a wave of heroin-related deaths, which began accelerating in 2011 as the medical community became increasingly alarmed by the role of prescription opioids in fostering the epidemic and began to institute professional and regulatory controls. By 2015, heroin deaths had surpassed the number of prescription opioid deaths. Opioid pill users are known to transition to readily available and lower-cost heroin as their growing opioid dependence outstrips their ability to obtain an increasingly larger supply of pills by prescription or on the street. More recently, a third wave of opiate overdose mortality has emerged due to illicitly produced fentanyls adulterating the heroin supply or being substituted for heroin (also known as "FASH"), particularly in the Northeast and Midwest. Since 2013, illicit fentanyls and other synthetic opioids have rapidly risen as a cause of overdose-related death, reaching a peak of over 28,000 deaths in 2017, compared to 15,000 deaths in 2017 in each of the other opioid categories (i.e., prescription opioid pills, heroin) [6].

As tracked by the Centers for Disease Control and Prevention (CDC), the overall prescribing rate for opioids leveled off from 2010 to 2012 and has been declining since, with a more than 19% reduction in annual prescribing rate from 2006 to 2017 [6], suggesting that the educational and regulatory efforts noted above have had some efficacy. However, in 2017, roughly 60 opioid prescriptions were written for every 100 Americans and more than 17% of Americans had at least one prescription filled [7]. With the consequences of opioid reliance well-documented, costing lives and livelihoods throughout America's history, additional pain management strategies are clearly needed.

What is Cannabis? Potential Mechanisms of Analgesia

As noted above, the use of cannabis as an adjunctive pain management strategy, both prescribed and non-prescribed, has increased markedly in the last decade. Multiple clinical and systematic reviews have proposed that cannabis may be an acceptable standardized treatment for chronic pain and that cannabis can potentially decrease opioid usage. We briefly review the physiologic evidence that makes this argument plausible.

Cannabis- more commonly known as marijuana -refers to the dried leaves, flowers, stems and seeds derived from the *Cannabis sativa* or *Cannabis indica* plant. Medical cannabis is an all-encompassing term that describes all serviceable cannabinoids and the vast assortment of cannabis products that can be consumed. The pain alleviating effect of cannabis is conferred by the therapeutic effects of cannabinoids, a group of substances found in cannabis extract. Two main cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD) [8].

In the 1990s, the targets, mechanisms and sites of action for these exogenous cannabinoids were identified as the endocannabinoid (EC) system. The EC system is comprised of the G protein-coupled receptors, CB_1 and CB_2, their endogenous ligands (anandamide [AEA] and 2- arachidonyl glycerol [2-AG]) and their associated synthetic and degradative enzymes (synthetic: N-acylphosphatidylethanolamine phospholipase D [NAPE-PLD] and diacylglycerol lipase α [DAGLα]; degradative: fatty acid amide hydrolase [FAAH] and monoacylglycerol lipase [MAGL]). The components of the EC system are expressed throughout nociceptive pathways, including the periphery, the dorsal horn of the spinal cord, and in the supraspinal pain-associated regions of the brain. The EC system appears to be expressed ubiquitously-on both excitatory and inhibitory neurons, peripheral immune cells, and glial cells-in the central nervous system (CNS). EC activity can produce anti-nociceptive or pro-nociceptive actions depending on the site of expression and the underlying physiological state [9] and involved in several physiological functions of the body, such as immune modulation, inflammation, analgesia, appetite, and more [10]. CB_1 receptors are mainly concentrated in the CNS, with lesser concentrations present in peripheral tissue [9,10]. These receptors are found in axons and nerve

terminals but are not present in neuronal soma or dendrites; this presynaptic presence of receptors is consistent with inhibitory functions in the CNS [11]. In contrast, the CB_2 receptors are primarily located in immune cells, but do have an inducible presence in sensory neurons and the spinal cord in response to neuropathic and inflammatory pain in animals [12].

THC has been found to act as a partial agonist at CB_1 and CB_2 receptors, therefore its effects are influenced by the dynamic expression of cannabinoid receptors [13,14]. Rat models show a higher CB_1 receptor concentration in the substantia nigra, globus pallidus, and lateral caudate-putamen and a higher G protein-coupling efficiency in the hypothalamus compared to the frontal cortex or cerebellum [15]. CB_1 receptors are distributed within the mammalian brain in a species-dependent fashion, with human brains expressing more CB_1 receptors in the cerebral cortex and amygdala compared to the cerebellum (6,7) [14,15]. These differences in expression help to explain the increased effect of CB_1 agonists on motor function in rats compared to humans [16].

Both the CB_1 and CB_2 receptors have been implicated in pain management, with development of various CB_2 -selective agonists demonstrating antinociceptive effects [17]. These agonists mediated pain sensitization in rat models in both naïve and sensitized subjects, at various dosing tiers. Some CB_2 agonists such as HU308 and AM1241, even at high anallgesic doses, do not show the centrally-mediated side effects seen with activation of CB_1 receptors, such as hypoactivity and catalepsy, suggesting that CB_2 agonists may not be psychoactive or addictive [18]. Recent studies also utilize peripherally restricted cannabinoid agonists to isolate analgesic effects from CNS side effects, specifically to explore the range of utility of CB_1 receptor stimulation [19]. There is evidence to suggest anti-allodynic effects mediated by the CB_1 receptor providing relief in the context of chemotherapy-induced peripheral neuropathy [19]. Electrophysiological data show that CB_2 agonists can suppress nociceptive responses in conditions where these nociceptive neurons are sensitized, such as persistent pain states [17,20]. Though these findings are promising to link cannabinoids to pain relief in a variety of chronic pain states, more research is still needed to expand outside animal models and be able to isolate both CB_1 and CB_2 agonism in vivo.

Legalization and the Rise of Medical Cannabis Use

The medicinal properties of cannabis and its components have been the subject of research and heated debate for several decades. In the United States, under the Controlled Substances Act of 1970, the use and possession of cannabis for any purpose is illegal under federal law. Under this Act, cannabis is classified as a Schedule I substance, defined as having no currently accepted medical use and a high potential for abuse [1]. However, policies at the state level regarding medical and recreational use of cannabis vary greatly, conflicting significantly with federal law.

Decriminalization is the cessation of legal or criminal punishments for the use or possession of a substance. However, decriminalization of cannabis does not remove its status as a controlled substance [21]. As of this writing, 25 states and the District of Columbia have either fully or partially decriminalized recreational, non-medical possession of cannabis. It is important to note that in states where cannabis is partially decriminalized, the law still classifies marijuana possession offenses as criminal, but the offenses do not carry threat of jail time [22].

Legalization, on the other hand, is the process of removing all legal prohibitions, allowing cannabis to be available to the adult general population for purchase and use at will, similar to tobacco and alcohol [23]. Currently, a total of 36 states and the District of Columbia have legalized the medical use of cannabis [24]. Although cannabis remains a Schedule 1 drug, the Rohrabacher-Farr amendments prohibit federal prosecution of individuals complying with state medical cannabis laws. As such, cannabis is now used to treat a wide range of chronic conditions, including neuropathic pain, fibromyalgia, glaucoma, anxiety, insomnia, post-traumatic stress disorder, epilepsy, depression, nausea and many others [25]. Furthermore, 17 states and the District of Columbia have legalized cannabis for recreational use [22].

Given the steady increase in the number of states liberalizing cannabis laws, the prevalence of medical cannabis continues to rise. A 2020 Gallup poll showed that a record high 68% of American adults were in favor of marijuana legalization [26]. Several surveys conducted over the last decade also show an increased willingness of patients to substitute cannabis in place of prescription drugs for pain management [27-29]. Studies demonstrating lower rates of opioid prescriptions in states with implementation of both medical cannabis laws and adult-use cannabis laws also contribute to the increasing popularity among both providers and patients [30]. At the very least, increasing legalization offers the prospect of more thorough and exacting laboratory, pre-clinical, and clinical research, as well more open conversations among clinicians and between clinicians and patients, as well as increased public revenue from taxation, as is the case with tobacco and alcohol.

The Efficacy of Cannabis for Treatment Chronic Pain

As noted above, attitudes in the US toward the medical utility of cannabis are evolving rapidly [31].However, what little peer-reviewed scientific evidence exists for the efficacy of cannabis and its derivatives in the treatment of chronic pain ranges from suggesting large effect [32], modest effect [33,34] , to no effect at all [35]. A major factor in this confusion is that research capable of generating Level 1 evidence for the safety and efficacy of the use of cannabis-equivalent to the standards brought to other medications and vaccines-is limited by current federal law. Study designs, patient populations, standards and quality of laboratory support for research, are all impacted by the legal status of the drug [36,37]. Several reviews report that cannabis may have particular usefulness in the treatment of neuropathic pain conditions [38-53]but note that existing studies are methodologically limited, and the long-term effects of cannabis are unclear [44]. The most inclusive of recent reviews of cannabis in pain management is a 2018 Cochrane review by Mücke, et al [41].This includes 16 studies with 1750 patients. Overall, these authors conclude

as a general statement that cannabis appears to have some association with pain reduction but is also associated with adverse effects may be limiting or outweigh benefit.

Some work has been done the utility of cannabis in the treatment of pain associated with fibromyalgia and rheumatoid arthritis [38,45-47], though good evidence remains scarce and severely limited by the usual methodologic concerns: diagnostic imprecision, small numbers, selection bias, and incomplete followup.

As yet, there has been minimal investigation of cannabis as an opioid-sparing adjuvant in pain management. As much of the literature has focused upon cannabis in comparison to placebo, evidence is sparse in comparison to opioid use. The largest prospective study of cannabis as a substitute for opioids was a 4-year cohort study of 1514 patients with chronic pain who had been prescribed opioids [49]. Cannabis was used in roughly 25% of these patients, and its use was associated with more subsequent pain, less self-efficacy for managing pain, and no reductions in prescribed opioid use. A systematic review of opioid-sparing effect of cannabinoids echoed this result with only one of nine studies included showing very low quality evidence of any benefit [50].

Conversely, taken at a population level, trends of reduced opioid use and overdose deaths [51] have been reported across some regions with the introduction of medical cannabi [51]. Prescription data from Medicare Part D enrollees in states with access to medical cannabis suggest a significant reduction in national opioid prescriptions [52]. States with medical cannabis laws, operating with state dispensaries, noted a decrease in hydrocodone use of 17.4% and a decrease of morphine use of 20.7% after the ratification of the medical cannabis laws, and several surveys of current opioid users in the US and Canada note self-reported decreases in opioid use with the availability of marijuana [54,55,56]. However, in the US, the scheduling of hydrocodone was also changed over the time period which may also have contributed to reductions. Growing evidence of opioid harms, increasing opioid prescribing guidelines, and trends away from opioid utilization may also impact this data. The same trend held true for a Medicaid sample, yet with smaller reductions in opioid prescriptions [29]. In a New York population of HIV patients, cannabis was the only variable in a multivariate analysis that was associated with a lower odds of prescription opioid use [56]. Conversely, data from Colorado show a steady rise in opioid and heroin overdose deaths in data collected through 2017, despite medical cannabis laws in place for nearly two decades [57] .

Comparative Risks of Opioids vs Cannabis

Opioids

The physiology of opiate tolerance that drives increasing demand and addiction has been explored intensively at the molecular, neurophysiologic, and pharmacokinetic levels for much of the last 50 years, and the personal, public health, and public safety costs of addiction are well known. In addition, however, clinicians caring for patients in chronic opioid treatment confront an array of additional adverse effects associated with acute and chronic opiate exposure. Slowing of gut peristalsis is associated with nausea, vomiting, and constipation that may be refractory to stool softeners and laxatives [58-60]. Respiratory depression is a key factor in fatal opiate overdose [60a] but may also be associated with sub-lethal effects including sleep-disordered breathing, decreased alertness, and increased risk of falls and fractures [61]. Direct effects on the central nervous system can include dizziness and sedation. Chronic opioid therapy has also been associated with dysregulation in the hypothalamic-pituitary-adrenal axis [61] and with direct cardiotoxicty [61]. Not surprisingly, opioid use is associated with increased risk of depression, anxiety, comorbidities with other substance use disorders, and increased pain sensitivity [62].

Cannabis

What is known about the molecular physiology of cannabis and its derivatives at the present time suggests that this family of neuro-active agents acts very differently than opiates and has far more limited potential for physiologic addiction, dose escalation, and lethal overdose [49,54]. However, the use of cannabis to treat chronic pain has not been without its own risks for adverse effects. Most of these center on the central nervous system. Multiple structural and functional abnormalities of the central nervous system have been documented with heavy use, including hippocampal atrophy, and a detrimental effect on verbal learning and memory [63]. Non-specific central nervous system symptoms like sedation and dizziness are common [64]. Neurocognitive deficits have been documented after 7 days of heavy use, as have potential structural and functional alterations in the brains of heavy cannabis users; long-term cognitive effects of cannabis use remain uncertain [54,64]. Increased risk for motor vehicle accidents associated with cannabis intoxication has been documented [44], most having to do with reaction time. There appears to be some increased risk for psychosis and mania; the association between cannabis use and psychosis has been found to be relatively consistent across studies [44]. Though less predictably than opiates, chronic cannabis use can cause dependence and can be associated with withdrawal symptoms similar to other non-narcotic substances of abuse like tobacco and alcohol. Other serious side effects can include cannabinoid hyperemesis syndrome, hepatotoxicity, pancreatitis, increased heart rate and blood pressure. Those who dose by inhalation, smoke or vape, have increased risk of acute and chronic pulmonary pathology [63,65].

Cannabinoids and substance use disorder

According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), a distinguishing feature of a substance use disorder involves continued use of a substance despite significant problems related to the ongoing use of that substance. The maintenance of a substance use disorder may involve changes in brain circuitry persisting beyond even detoxification from the substance in question, manifesting in repeated relapses or intense cravings for the drug; as such, diagnosis of a *substance use disorder* is based on identifying pathological behavioral patterns indicating impaired control,

social impairment, risky use, and/or pharmacological symptoms such as tolerance and withdrawal [66].

Regular cannabis use can lead to an individual developing all the characteristic features indicative of a substance use disorder. Cannabis use disorders can occur individually but may also frequently co-occur with other types of substance use disorders, such as alcohol or opioids [67]. At the present time, cannabis is the most prevalently used illicit substance in the United States, with 12-month and lifetime prevalence rates for cannabis use disorders of approximately 2.5% and 6.3%, respectively [31,52,66]. Regular cannabis use at an early age, particularly before the age of 15, has been found to increase risk for developing problems with cannabis use later in life, particularly among adolescents with oppositional or antisocial behaviors, as well as adolescents with poor school performance [64,66]. Males, in both adult and adolescent populations, are at a higher risk for developing cannabis use disorders [66,67]. Not surprisingly, the increased availability of cannabis in recent years, as discussed above, appears likewise to be associated with an increase in the prevalence of cannabis use disorders [31,68].

Given the abuse potential of both opioids and cannabis, concerns have arisen that clinicians may simply be treating one substance dependence by replacing it with another, likening the promotion of cannabis in chronic pain treatment to the history of the medical use of opiates and noting that medical detoxification by substance substitution has limited long-term efficacy [69]. Unfortunately, simplistic arguments complicate full engagement with the social and pathophysiologic complexities of addiction disorders. Medical cannabis users do appear to be at higher risk for nonmedical prescription drug use, including stimulant and tranquilizer medications, as well as pain relievers [70]. Co-use of cannabis and opioids among chronic pain patients has been associated with depression, anxiety, opioid misuse and dependence, along with problems related to alcohol, tobacco, cocaine, and sedatives [71], though, as in every other aspect of cannabis research, the history of legal restraints and the general paucity of reliable evidence distorts useful professional conversations and development of reasonable guidelines on these issues [72].

Summary and conclusions

For selected individuals, cannabis and its derivatives appear to have some efficacy in mitigating chronic pain, but the long history of these substances in the US as illegal and counter-culture substances has severely hampered rigorous research and the development of reliable, Level 1 evidence for their use in pain medicine practice. Owing to this paucity of good evidence, the safety and efficacy of cannabinoids in reducing opioid use and dependency and the generalizability of their use remain open questions. Experienced pain medicine physicians working closely with carefully selected [54], well-known, well-counseled patients, are now increasingly able to consider cannabinoids as part of their armamentarium against chronic pain and opioid dose escalation. Unfortunately, serious, federally-funded research still faces the obstacle course of studying a Schedule I controlled substance, which in itself may distort results [73-76]. Until these public policy issues are settled in favor of good science, these questions are likely to remain open.

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DOI: 10.36959/377/370