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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Medical Cannabis for Chronic Nonmalignant Pain Management

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Abstract

Purpose of Review Cannabis has been used since ancient times for medical and recreational research. This review article will document the validity of how medical cannabis can be utilized for chronic nonmalignant pain management.

Recent Findings Current cannabis research has shown that medical cannabis is indicated for symptom management for many conditions not limited to cancer, chronic pain, headaches, migraines, and psychological disorders (anxiety and post-traumatic stress disorder). Δ9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) are active ingredients in cannabis that modulate a patient's symptoms. These compounds work to decrease nociception and symptom frequency via the endocannabinoid system. Research regarding pain management is limited within the USA as the Drug Enforcement Agency (DEA) classifies it as a schedule one drug. Few studies have found a limited relationship between chronic pain and medical cannabis use.

Summary A total of 77 articles were selected after a thorough screening process using PubMed and Google Scholar. This paper demonstrates that medical cannabis use provides adequate pain management. Patients suffering from chronic nonmalignant pain may benefit from medical cannabis due to its convenience and efficacy.

Keywords Cannabis · Medical marijuana · Chronic nonmalignant pain · Opioids

This article is part of the Topical Collection on *Alternative Treatments for Pain Medicine*

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Introduction

Due to its association with decreased quality of life, opioid dependence, and negative impact on mental health, chronic pain is a common reason adults seek medical attention. Chronic pain is assessed through the experience of patients, who, when asked, "how often have you experienced pain in the past three months?", respond with "most days" or "every day." According to the Centers for Disease Control and Prevention (CDC), in 2019, approximately 20.4% of adults in the USA had chronic pain, while 7.4% reported high-impact chronic pain. Chronic pain was highest among females (8.5%) and patients aged ≥ 65. Non-Hispanic adults experienced more chronic pain (23.6%) and high-impact chronic pain (8.4%) in the past 3 months compared to their Hispanic and non-Hispanic Black/Asian counterparts [1].

The current standard of treatment for chronic pain involves opioid analgesics, which can be problematic due to side effects ranging from severe constipation to respiratory depression and opioid dependence. The opioid epidemic poses a formidable challenge. The World Health Organization (WHO) estimates that approximately 0.5 million deaths yearly are attributable to drug use; more than 70% are due to opioid use [2]. Compounds derived from the *Cannabis sativa* and *Cannabis indica* plants have been studied and seen to have a therapeutic role in pain management while simultaneously decreasing opioid prescriptions among patients with long-term conditions such as chronic kidney disease [3, 4].

In 1996, the California Compassionate Use Act was among the first state policies legalizing the use of cannabis (primarily in the context of analgesia and antiemesis in patients with AIDS) [5]. California was the first state in 1996 to legalize the California Compassionate Use Act, which allowed for the use of cannabis (primarily in the context of analgesia and antiemesis in patients with AIDS) [5]. Thirty-eight US states and the DC in 2017 permitted the use of medical cannabis [6], with more than 2.1 million people with medical cannabis licenses in the legalized medical cannabis states. Out of these licensed individuals, 62% had chronic pain accounting for the license-qualifying condition throughout the USA [7]. Both tetrahydrocannabinol (THC) and cannabidiol (CBD) are commonly used for chronic pain management in patients with advanced cancer, chronic pelvic pain, multiple sclerosis spasticity, fibromyalgia, and sleep apnea, as well as for adjunctive traditional analgesic therapy [8–10]. In the USA, Canada, and the Netherlands, chronic nonmalignant pain is the most cited reason for the use of cannabis for medical purposes [11••]. The present review attempts to highlight the benefits, use, forms, and limitations of cannabis use in managing chronic pain and see how it compares to opioids for a conclusive treatment approach.

Mechanism of Action

Cannabis, also known as marijuana, has an age-old history of recreational uses but is increasingly getting substituted with opioids for pain therapy. Multiple molecular and preclinical studies have been performed that support the antinociceptive role that cannabis plays [12, 13]. However, in the human picture, there is a lack of strong evidence for us to use cannabis-based medications in broad clinical practice as pain therapy [14].

The endocannabinoid system (ECS) is believed to play an integral role in pain modulation. It works by various mechanisms involving neuro- and immuno-modulation at the supra-spinal, spinal, and peripheral levels [15–17]. The enzymes responsible for the synthesis, metabolism, and regulation of the endocannabinoid ligands, along with the cannabinoid receptors (CB1/CB2), comprise the endocannabinoid system [15–18]. There are three broad categories of cannabinoids that are accepted in the literature: endogenous cannabinoids, which are derived from arachidonic acid, phytocannabinoids (THC and CBD), which are derived from the cannabis plant (*Cannabis sativa*), and synthetic cannabinoids (dronabinol and nabilone), which are artificially produced compounds targeting various elements of the endocannabinoid system [16, 19].

Endocannabinoid Receptors

A class of endogenous ligands derived from arachidonic acid that exert their effect on the cannabinoid receptors is termed endocannabinoids. This group's major lipid mediators are arachidonoyl ethanolamide (anandamide or AEA) and 2-arachidonoylglycerol [20]. Palmitoylethanolamide (PEA) and oleoyl ethanolamide (OEA) are structural analogs also belonging to endocannabinoids that interact with nuclear receptors (PPARs and TRPV1) and G- protein-coupled receptors (GPR55, GPR92, and GPR18) [21, 22]. These ligands are involved in several physiological systems including mood, memory, satiety, female reproduction, immune, gastrointestinal, cardiovascular system, and pain (including neuropathic) [15, 20].

Cannabinoid receptors CB1 and CB2 are present in neurons throughout the central and peripheral nervous system; they act on immune and non-neuronal cells in both the central and peripheral nervous system and work through modulation of G-protein-coupled receptors (GPCR) [8, 23]. CB1 receptors can be located in the CNS, presynaptic terminals of peripheral pain receptors, neurons in the dorsal root ganglion, smooth muscle, adipocytes, spinal cord, and myocardium [24]. In contrast, CB2 receptors are present in the non-neuronal cells of CNS (macrophages, microglia,

and astrocytes) and organs with immune and hematopoietic function (leukocytes, spleen, tonsils, lung, testes, and brain) [19, 23, 25].

It is hypothesized that CB1 receptors inhibit excessive neuronal excitation and activity and thus maintain homeostasis [26]. By binding to the CB1 presynaptic receptor, cannabinoids inhibit the calcium influx, decreasing the release of neurotransmitters and thereby decreasing/modulating pain [27]. The primary neurotransmitters inhibited by activation of the CB1 receptor are γ-aminobutyric acid (GABA) and glutamate; albeit acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine (5-HT), D-aspartate, cholecystokinin, and others have also been found to play a role [27]. CB1 receptors also have a role in the spinal and supraspinal levels by suppressing nociception in the spinal cord dorsal horn and activating descending inhibitory pathways in the raphe nucleus periaqueductal gray. In contrast, activation of the CB2 receptor reduces inflammation pain. It causes hyperalgesia through complex interactions within the ECS system and altered release of pro-inflammatory cytokines like interferon-gamma, interleukins, and tumor necrosis factor-alpha [25–27].

Different Forms of Cannabis and Patient Preferences

Many existing studies in the broader literature have reviewed different forms of cannabis used by patients suffering from chronic pain. In 2021, Lovecchio et al. conducted an online survey on 214 patients with spine-related chronic pain. The study reported that only 25.2% of patients used medical cannabis for potential pain relief. More males (58%) participated in the survey than female patients. Analysis of consumption patterns revealed that the most common formulations used by patients were oil and tincture (65%), with topical creams (37%) and edible methods (33%) being the next most common. This paper also reported that approximately one-thirds of patients (19 out of 54) used more than one form [28].

A recent cross-sectional study was conducted by Fitzcharles et al. to examine the prevalence and characteristics of medical cannabis use in fibromyalgia patients in Canada. Patients were asked about previous and current cannabis use, frequency, method of use, the daily amount used in grams, and the reason for discontinuation, if applicable. From the survey, 28 (23.9%) of fibromyalgia patients had tried medical cannabis to treat their chronic pain, with more than half reporting continued use. Of the current users, cigarette smoking was the primary method of use, followed by vaporization, oil capsules, and cannabis-infused food (i.e., edibles) [29].

In an observational prospective cohort study by Meng et al., patients with chronic pain seeking medical cannabis were investigated. Each patient was required to fill out a baseline questionnaire on their initial visit and follow-up questionnaires at 3, 6, and 12 months. A total of 757 participants completed baseline questionnaires. The majority of them were females (61.6%). At baseline, the most common form of use was dried cannabis (68.2%); however, the combination of dried cannabis and cannabis oil became consumed most commonly [30].

In a 2021 survey by Schilling et al., participants were asked about their demographics, awareness, experience, and knowledge of CBD. Participants were also questioned regarding the type of products they used, choosing more than one form of use. Inhaled/smoked products were the most common type of products used (62.9%), followed by edibles (54.3%), oral tinctures (52.3%), ointment/oil, and cream (49.7%) [31].

Vidot et al. (2020) conducted a cross-sectional study in the USA to analyze the patterns of cannabis use among medical cannabis users with chronic conditions and how those changed due to the COVID-19 pandemic. A total of 1202 participants completed an online-based questionnaire (52% were males). The most common routes of administration were inhalational and as follows: smoking (39%), vaporization (24.1%), and smoking via joints (without tobacco) (18.8%). The results also reported that 16% of participants changed their route of administration due to the pandemic. In comparison, after the declaration of COVID-19 as a pandemic, the nonsmoking route was the most common administration method: edibles (31.4%), tinctures (10.9%), and pills (4.2%). This route is primarily attributed to the fact that many inhalational smokers (59.2%) have stopped sharing their cigarettes and electronic vaporizing devices since the declaration of the pandemic [32].

In a 2020 cross-sectional study conducted by Sznitman et al., 125 adult chronic pain patients participated in the survey (51.2% were females). When asked about the modes of cannabis administration they use, survey participants, who could indicate multiple preferences, reported smoking (68.6%) as the most common route, followed by oil extracts (21.4%) and vaporization (20.0%) [33].

Most persons with chronic pain choose a combination of indica and sativa to alleviate their symptoms [34]. Males and females, those who solely used cannabis for medical reasons and those who supported both medical and recreational use, and rookie and expert users all had similar cannabis strain preferences [34].

The majority of patients preferred medical cannabis products with balanced THC: CBD ratios (37%) or high CBD formulations (46%) and only a minority (17%) preferring high THC products (moderate certainty) [35]. Women, rookie users, and those who solely endorsed cannabis for medicinal purposes preferred products with low THC and high CBD ratios, whereas males, those who endorsed

cannabis for medical and recreational purposes, and experienced users chose products with equal THC:CBD ratios [36].

The preference for the route of administration was influenced by sex, the reason for usage, and previous cannabis experience (moderate certainty) [37]. Women preferred tinctures and topical medicines to vaporizing or smoking compared to male patients [36]. Compared to rookie users who favored vaporizing, experienced cannabis users endorsed several methods of administration [36]. Most patients with advanced life-limiting illnesses preferred oral (non-inhaled) medical cannabis preparations [38].

Legalization of Cannabis

The medical and recreational consumption of cannabis in the USA has a complex history of medical, legal, economic, and social aspects. Cannabis laws in states are closely tied to public perceptions [39]. In the last few decades, the perception that cannabis may not be harmful and has medical benefits has grown in society [40, 41]. Furthermore, support for the legalization of medical cannabis has increased significantly among health professionals and medical students [42].

As of 2021, 36 US states and the DC have passed laws legalizing medical, while 18 US states and the DC have passed laws regulating the legalization of recreational marijuana [6]. There are also medical cannabis programs in other countries such as Canada, Germany, Italy, Israel, the Netherlands, UK, Uruguay, Brazil, Colombia, and Thailand [43, 44]. Approximately 72% of the US population now lives in states where medical cannabis is legalized [6, 45]. About 10% of cannabis users in the USA use it to treat a medical condition [46].

Although many states have legalized medical, cannabis use still violates federal law. Cannabis, defined by the US Drug Enforcement Administration (DEA) as a schedule I substance, which means no currently accepted medical use, causes federal and state laws to become dichotomous [47]. Although the legalization of medical cannabis continues rapidly in the states, the DEA reaffirmed that marijuana is a schedule I substance in 2016 [48].

There are various arguments supporting and opposing the legalization of medical cannabis. Generally, these arguments are contradictory, positing that the legalization of medical cannabis will either increase or decrease marijuana use, provide stricter regulation, increase or decrease public safety, and more [49•]. Opponents argue that cannabis use in early adolescence is associated with future academic failure. Therefore, the possibility that marijuana use may increase in the younger age group is a constant topic of discussion [50].

There is a significant difference between non-legal and decriminalized states in calling poison centers for the pediatric age group [51]. Legalizing medical cannabis may increase the prevalence of marijuana use in the adult age group, but studies are mixed [51, 52]. In addition, many variables such as genetic differences of marijuana plants, variations in the prices, and the potency of the products are associated with the mixed results of studies in the medical literature [53]. Another critical question is how marijuana use will affect opioid use. Although studies show that marijuana legalization can reduce the opioid epidemic, research is conflicting [48, 54].

According to the states where medical cannabis is legal, cannabis is used for many diseases such as chronic pain, seizures, migraine, cachexia, spasticity, post-traumatic stress disorder, irritable bowel syndrome, inflammatory bowel syndrome, and glaucoma [55, 56]. However, the FDA has approved only dronabinol and nabilone (laboratory derived) for chemotherapy-related nausea and AIDS-related weight loss and cannabidiol (plant derived) for Lennox–Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex-associated seizures [40, 57].

The plight of the opioid epidemic has prompted physicians to seek other ways to manage chronic pain, and medical cannabis may be an alternative to opioids for chronic pain [58]. One of the most approved indications in states where medical cannabis is legalized and the most common reason for patients to demand cannabis is chronic pain [23, 58]. There is data that marijuana use is associated with decreasing prescription of other drugs for pain [52].

The increasing number of medical cannabis laws globally requires health professionals to know cannabis in medical, legal, logistic, and economic aspects. The illegality of medical cannabis at the federal level is an issue that needs to be discussed with patients, as legal complexity may arise in the circumstances such as crossing state borders [23]. Physicians should also discuss the economic facets of medical marijuana with patients, as medical cannabis is rarely covered by insurance [46].

Despite state and federal law dichotomy, physicians are legally protected under Conant v. Walter's decision as they suggest medical cannabis as a professional recommendation [55]. The unstandardized cannabinoid preparations, the lack of a common opinion on dosages, the little known about the side effect profile, and the lack of sufficient data on drug interactions appear as general discussions around legalization for medical purposes [58]. In particular, the use of medical cannabis for chronic pain can provide effective results for both pain management and slowing down the opioid epidemic.

Comparison with Opioids

Opioids have been the mainstay of intractable chronic pain management for a long time. However, the adverse effects of their use and increased mortality rates due to

their overdose are issues of concern. Cannabis extracts and their synthetic preparations slowly replace opioids for applications in various conditions involving chronic pain and inflammation [59]. In emerging studies, cannabis is as effective as or even better than opioids in relieving chronic pain of multiple origins [60••, 61, 62].

A meta-analysis conducted by Busse et al. found no difference in the extent of pain relief between opioids and nabilone, a synthetic cannabinoid (73 patients; mean difference − 0.13 cm [95% CI, − 1.04 to 0.77 cm] on the 10-cm Visual Analog Scale for pain, $P = 0.77$), indicating that cannabinoids could be as effective as opioids in pain relief [60••]. Another study conducted by Sohler et al. among HIV-infected individuals demonstrated that cannabis use was significantly associated with lower odds of opioid use as prescription analgesics (adjusted odds ratio = 0.57 (95% C.I. 0.38–0.87) [63]. These findings provide evidence regarding the efficacy of cannabis in mitigating pain alongside the widely prescribed opioids.

There, however, is limited evidence available to define standard comparable doses of cannabinoids and opioids to achieve the desired control of pain. One study by Noyes et al. attempted to compare the doses of tetrahydrocannabinol (THC) and codeine, wherein 10 mg of THC was slightly less effective than 60 mg of codeine, and 20 mg of THC was slightly more effective than 120 mg of codeine in controlling chronic cancer pain [64]. Another single-patient study observing the analgesic effects of oral 5 mg THC, 50 mg codeine, and placebo concluded that both drugs were significantly more effective than placebo in controlling multiple sclerosis-related pain [61].

Many studies have also shown that cannabis use has helped reduce opioid dependence greatly and that cannabinoids could be the next big substitutes for them, facilitating the global burden of increasing opioid addiction and fatalities. A survey performed by Boehnke et al. revealed that the use of medical cannabis was associated with a 64% reduction in opioid use in 118 subjects, minimized side effects of medications, and improved quality of life (45%) [65]. Another study performed to analyze the effect of cannabis on pain and quality-of-life outcomes in chronic pain found that along with the improvement in the pain severity score (7.50 [95% CI 6.75–7.75] to 6.25 [95% CI 5.75–6.75], $P < 0.001$), opioid consumption at follow-up decreased by 44% ($P < 0.001$) [66]. In an extensive study from Israel encompassing 3619 participants, only 4.6% continued to experience severe pain (> 7/10) after 6 months of cannabinoid mixture administration compared to 52.6% at baseline. The use of opioids ceased in 36% of patients, a decrease in opioid doses was reported by 10% of patients, and an opioid increase was reported by only 1% of patients [67].

Opioids have adverse effects in much greater proportion than cannabinoids. Most patients experience gastrointestinal or central nervous system-related adverse events, most commonly constipation, nausea, and somnolence. Cognitive impairment and dizziness are less prevalent but reported [68]. Dependence and respiratory depression are effects of even more concern. On the other hand, cannabinoids usually have various temporary side effects, which eventually subside with the development of tolerance. Vomiting, urinary tract infection, or even relapse of multiple sclerosis has been reported in a systematic review by Wang et al. as some serious side effects [69]. THC, a psychoactive constituent of cannabis, has been implicated in cardiovascular disease, acute pancreatitis, cannabinoid hyperemesis syndrome, and particularly in pregnancy, and is associated with an increased risk of neonatal morbidity and death [65, 70].

Conclusions

Patients often seek medical consultations most commonly because of having intolerable chronic pain. Medications such as NSAIDs or opioids are being used to relieve such pain. However, long-term use of these medications can also cause adverse effects on health. Several studies have been done regarding cannabis as an alternative for chronic pain. Some patients were reported to get relief from cannabis consumption through various routes, and the use of it has been legalized, too, in some states in the USA and countries like Germany. Italy, the Netherlands, UK, Australia, Uruguay, Brazil, Colombia, Chile, Thailand, and Jamaica. Compared with opioids, studies show that cannabis use has lesser adverse effects, and it could even lessen opioid dependence. As clinicians, it is good to determine the primary purpose of using cannabis before prescribing it to patients to weigh the advantages and disadvantages that underlie it. Evaluating patients very well about the use of cannabis is important to decide whether to prescribe such medication or just sort to other alternative ways of managing pain to render the best possible patient care.

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Data Availability The authors declare that data supporting the findings of this study are available within the article.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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- • Of importance
- •• Of major importance

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