Cannabinoids and Pain

The Highs and Lows

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KEYWORDS

• Marijuana • Cannabinoids • Chronic pain • CBD • THC

KEY POINTS

- Cannabinoids can be effective at treating some chronic pain.
- There is limited high-quality evidence regarding the use of cannabinoids in pain.
- Cannabinoids have opioid sparing properties and can be useful in treating pain.
- CBD may be useful in treating anxiety and improving sleep.

INTRODUCTION/BACKGROUND

Cannabis has been used medicinally for the treatment of pain for millennia, but its use in modern medicine has been encumbered by what can be described as an excess of public enthusiasm, a relative paucity of rigorous trials, and a minefield of politicization and regulatory challenges. Regardless of these challenges, the landscape of cannabis use is rapidly expanding, at least in the United States, with state legislatures adopting decriminalization and legalization above-and-beyond any purported therapeutic use within the medical setting. Because of this it is imperative that clinicians remain well versed in the literature to better explain and answer questions their patients might have about the relative benefits (and oft-ignored harms) of cannabis and its various pharmacologically active compounds. Specifically, we seek to separate the high from the hype with the hope that we can ground expectations regarding the use of cannabinoids in the treatment of pain.

RELEVANCE

Chronic pain is frequently stated as the primary reasons for the use of medical cannabis. In Colorado, 94% of marijuana identification holders indicated "severe pain" as a medical condition.[1] An earlier study evaluating patient characteristics in

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2013 found that 87% of patients seeking medicinal marijuana cited using it for analgesia.[2] The demand for cannabis in the treatment of pain precedes formal approval by the United States Food and Drug Administration. Observational studies have shown that states with access to medical marijuana have had an associated reduction in the number of prescribed opioids and benzodiazepines.[3,4] With legalization of medical marijuana, patients are increasingly turning to marijuana as a potential treatment of their pain. The heterogeneity of cannabis compounds available on the marketplace ranging from synthetic and plant-based formulations, the varying routes of delivery (oral, smoke inhalation, vaping, topical), and the lack of standardization for dosing and quality increases the difficulty of researching cannabis and its cannabinoids. Most of the individual use is not representative of the cannabinoids studied in the currently available standardized trials.

CANNABINOIDS AND THEIR RECEPTORS

Cannabis is a genus of plants that includes *Cannabis sativa* that produce more than 500 compounds of which 107 are classified as phytocannabinoids.[5] Cannabinoids can be divided into 3 groups: phytocannabinoids, which are derived from the plant cannabis, endocannabinoids, which are endogenous compounds capable of interacting at cannabinoid receptors, and synthetic cannabinoids, which have been manufactured as pharmacologic products.[6] The primary psychoactive compound is the phytocannabinoid Δ9-tetrahydrocannabinol (Δ9-THC), which was isolated in 1967.[7] Outside of Δ9-THC, there are other important pharmacologically active phytocannabinoids including delta-8-tetrahydrocannabinol (Δ8-THC), cannabidiol (CBD), and cannabinol.[6] CBD is the second most abundant phytocannabinoid in cultivated marijuana and is minimally psychoactive but plays an important role in modulating the effects of other phytocannabinoids.[8] The primary endocannabinoids are anandamide (AEA) (ananda is Sanskrit for “bliss”) and 2-arachidonoylglycerol (2-AG) [9](**Table 1**).

Cannabinoids function through binding to 2 receptors: the cannabinoid receptor type 1 (CB1) and CB2.[10] Both CB1 and CB2 function through the action of G protein–coupled receptors, which when agonized leads to the inhibition of adenylyl cyclase.[11] The 2 receptors, CB1 and CB2, and their associated ligands, anandamide and 2-arachidonoylglycerol, form the endocannabinoid system. CB1 receptors are commonly found throughout the central nervous system, whereas CB2 receptors are less widely distributed but can be found on immune and hematopoietic cells and play an important role in cytokine regulation.[12] CB1 receptors are most commonly presynaptic, and their stimulation via endocannabinoids leads to suppression of neuronal excitability, which inhibits neurotransmission.[13] This inhibition and the widespread distribution of CB1 receptors through the central nervous system suggests that the underlying function of the endocannabinoid system may be to suppress excessive neuronal activity through modulation of inhibitory and excitatory

Table 1
Cannabinoids and their receptors

Endocannabinoids	Phytocannabinoids	Synthetic Cannabinoids
Anandamide (AEA)	Tetrahydrocannibinol (THC)	Dronabinol
2-Arachidonylglycerol (2-AG)	Cannabidiol (CBD)	Nabilone
	Cannabichromene (CBC)	Lenabasum
	Cannabigerol (CBG)	

neurotransmitters, including acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine, g-aminobutyric acid, glutamate, D-aspartate, and cholecystokinin.[8,11] There is evidence that phytocannabinoids such as Δ9-THC may directly affect other receptors, with several studies finding it functions as a partial agonist on mu-opioid receptors.[14–16] In addition, cannabinoids acting at CB2 receptors have been shown to directly increase release of endogenous opioids.[17] This likely accounts, at least in part, for the opioid-sparing effect seen with coadministration of cannabinoids.[18]

In contrast to the agonism that Δ9-THC has on CB1 and CB2, the role of CBD is distinctly different. Notably, CBD has low affinity for CB1 and CB2 but has demonstrated activity as an antagonist and "inverse agonist" with meaningful downregulation of CB2, which has been shown to contribute to an antiinflammatory effect by modulating cytokine release.[8,19] CBD may indirectly affect pain via antiinflammatory and anxiolytic properties. One potential mechanism of action is the purported CBD inhibition of fatty acid amide hydrolase, the enzyme hydrolyzing the endocannabinoid N-arachidonoylethanolamine (AEA). Boosting AEA levels may be a therapeutic strategy, as evidenced in animal studies and in one human study of CBD for psychosis in patients with schizophrenia.[20,21]

Δ9-THC has antinociceptive effects through agonism of CB1 and CB2 cannabinoid receptors, located centrally and peripherally.[22,23] CB2 inhibits the inflammatory pain response, indirectly activates opioid receptors via primary afferent pathways, and is upregulated in neuropathic pain at the dorsal root ganglia.[17,24] THC has been shown to be an effective analgesic and has antinociceptive synergy when combined with opioids, providing opioid-sparing effects.[18,25–28] The analgesic mechanisms of CBD remain poorly understood and may be occurring at noncannabinoid receptors.[29]

PHARMACOLOGY OF CANNABINOIDS

The pharmacokinetics of cannabinoids depends on formulation and method of administration. Inhalation is equivalent to intravenous administration in terms of time to peak plasma concentration of both THC and CBD with a time to peak concentration ranging between 3 and 10 minutes.[30] When inhaled, THC has a bioavailability of 10% to 35% (the wide range is secondary to the variability related to inhalation technique and the device), and CBD has a similar bioavailability of 31%.[30] This is in contrast with oral absorption wherein there is first-pass metabolism of both THC and CBD with a bioavailability of about 6% and delayed peak plasma concentration of 60 to 120 minutes.[30,31] The substantial delays in oral administration account for many of the difficulties in self-titration with edible THC products. Oromucosal administration avoids these effects and has similar characteristics to inhalation with some delay likely secondary to oral ingestion. The metabolism of THC is hepatic via cytochrome p450 isozymes CYP2C9, CYP2C19, and CYP3A4; similarly, CBD is hepatically metabolized via CYP2C19 and CYP3A4, and both are excreted in the urine and feces.[30] Notably, THC is highly lipophilic and is able to cross the placenta and is excreted into breast milk.[32]

PHARMACOLOGIC OR MEDICAL TREATMENT OPTIONS

In addition to herbal marijuana, there are several pharmaceutical preparations containing cannabinoids: nabiximols (Sativex), dronabinol (Marinol), nabilone (Cesamet), and plant-derived CBD (Epidiolex).

Herbal marijuana is a heterogenous source of cannabinoids, posing a challenge in evaluating its clinical efficacy. It is primarily smoked and inhaled but can also be consumed orally, vaporized, or applied topically. The concentration of Δ9-THC and CBD varies substantially between plant strains, growing environment, and product

preparation. A recent evaluation of cannabis grown and sold at dispensaries in the United States found the average Δ9-THC concentration to be greater than 24% with a corresponding decrease in CBD concentration as Δ9-THC increased.[33] A recent study in JAMA evaluating labeling of cannabinoid containing products at dispensaries found that approximately 17% were accurately labeled with regard to THC content; of the products evaluated there was a mean THC:CBD ratio of 36:1, a THC ratio that is higher than what has been studied previously.[34] These higher concentrations of Δ9-THC are distinct when compared with the currently available literature, demonstrating efficacy in the treatment of neuropathic pain with concentrations of Δ9-THC ranging from 5% to 10%.[25,35,36] As the Δ9-THC content increases the rate of adverse side effects increase, with some studies demonstrating a dose-dependent *hyperalgesic effect*.[37,38] Inhaled medical cannabis containing both Δ9-THC and CBD has been shown to decrease treatment refractory neuropathic pain in a dose-responsive manner.[25,37,38]

Nabiximols (Sativex) is a whole plant–derived oromucosal formulation of a 1:1 ratio of THC:CBD approved in Canada and several European countries for the treatment multiple sclerosis (MS) related.[39] Its formulation allows for a consistent dose of 2.7 mg of THC and 2.5 mg of CBD per spray, with rapid onset of effects occurring within 15 to 40 minutes allowing for titration to effect. The combination of CBD and THC seems to balance the partial agonism of CB1 and CB2 with an antagonistic effect from CBD, which serves to amplify some of the beneficial effects while ameliorating many of the adverse effects with evidence suggesting it also reduces the risk of dependence.[40] Sativex has been well studied in MS, demonstrating a reduction in MS-related spasticity, MS-related pain, and improved sleep.[41–43] Outside of MS, there have been 2 trials involving neuropathic pain, one involving brachial plexus avulsion and another involving unilateral neuropathic pain, where Sativex was found to substantially reduce pain and improve quality of sleep.[44,45] It is currently not approved by Food and Drug Administration (FDA) in the United States but is undergoing phase III trials for it therapeutic efficacy in cancer-related pain.

Dronabinol (Marinol) is a synthetic form of delta-9-THC that is FDA approved for the treatment of nausea associated with chemotherapy and used as an appetite stimulant for human immunodeficiency virus (HIV)-related wasting syndrome.[8] Dronabinol has been studied as an adjuvant to opioid therapy in the treatment of chronic pain, with significant increase in pain relief and satisfaction.[46] Nabilone is another synthetic analogue of THC, which is more potent than dronabinol. It has been shown to have a modest effect on reduction of pain scores, with improvement of secondary outcomes including sleep and anxiety.[47] Both are currently FDA approved in the United States to treat chemotherapy-associated nausea and vomiting.

COMPLICATIONS

One of the greatest challenges facing the evaluation and use of cannabinoids in the treatment of pain is the associated side effects and potential for abuse and dependence. These effects are variable and dose dependent. THC can cause euphoria, dizziness, anxiety, tachycardia, dry mouth, decreased body temperature, hypotension, paranoia, somnolence, and impaired concentration and memory.[48] There is evidence that heavy use of cannabis increases the risk of psychosis and schizophrenia.[49,50] CBD, in comparison, has not been shown to have any significant side effects in humans either at high doses or with chronic use when studied in isolation.[51] When used in conjunction with THC, CBD has been shown to ameliorate the psychoactive properties of THC.[19,40,51] The frequency with which adverse effects occur is

very high, with a recent systematic review and meta-analysis in 2018 demonstrating that the OR of adverse effects was 2.33 (1.88–2.89) when compared with placebo with thought disturbance (odds ratio [OR] 7.35), dizziness (OR 5.52), and confusion listed as the most common adverse events.[52] It should be noted that most of the adverse effects are nonserious and that there are no substantiated reports of death from overdose of either THC or CBD.[51,53,54] In a 1-year prospective cohort trial titled Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS) medical cannabis users had no increased risk of serious adverse events when compared with placebo but did have a significant increase in nonserious adverse events.[55] An additional complication arising from marijuana use is dependence, with up to 8% of users of nonmedical cannabis developing dependence; however, this subject is not well studied within medical cannabis users.[56]

THE EVIDENCE FOR CANNABINOIDS AND PAIN

There are few high-quality randomized control trials evaluating the use of cannabinoids as they relate to pain, inflammation, sleep, and anxiety. Those that do exist predominantly address neuropathic pain, with relatively fewer studies addressing acute pain, inflammatory pain, and cancer pain. To date, the most comprehensive systematic review evaluating the medical use of cannabinoids was published by Whiting and colleagues[57] in 2015. The review included 28 randomized controlled trials (RCT) in patients with chronic pain including 2454 participants and found that the average number of patients who reported a reduction of neuropathic or cancer pain by at least 30% was greater with cannabinoids than with placebo with an OR of 1.4. Based on this systematic review, including a few smaller more recent trials, the National Academies of Sciences, Engineering and Medicine published a consensus study stating there was substantial evidence to support the use of cannabinoids in the treatment of chronic pain.[50]

In contrast to Whiting and colleagues, a systematic review by Stockings and colleagues in 2018 focused specifically on the use of cannabinoids in the treatment of chronic noncancer pain broadened the review criteria to include 47 RCTs and 57 observational trials including 9958 participants. The results found that 29% of participants taking cannabinoids compared with 25.9% using placebo reported a 30% reduction in pain with a number needed to treat of 24 and a number needed to harm of 6.[52] Their findings report there is no high-quality evidence to support the use of cannabinoids in chronic noncancer pain. A more focused systematic review in 2016 of RCTs evaluating the use of cannabinoids in the treatment of chronic pain associated with rheumatic disease including fibromyalgia, chronic spinal pain, and rheumatoid arthritis similarly found that there was insufficient evidence to support their use.[58]

Less is known about CBD and how it affects pain and anxiety. A preliminary crossover study of 24 patients reported that CBD was effective in treating neuropathic pain. However, this was a cannabis medical extract (called “CBD-rich”); it is possible the therapeutic benefit was from other natural phytocannabinoids.[59] There have only been 2 other prospective trials of CBD for pain in humans, with small data sets and incomplete analyses.[60,61] CBD has been shown to reduce anxiety in social settings, and this anxiolytic effect may indirectly account for improvement in pain.[62,63] Approximately 50% of patients with chronic pain have anxiety-potentiated, pain-related disability scores.[64] CBD has been shown to have a dose-dependent impact on increasing overall length of sleep, which may benefit patients with pain-related insomnia.[65]

The evidence regarding the use of cannabinoids in chronic pain is mixed and of low quality. Although some research suggests cannabinoids are helpful in cancer and neuropathic pain, further research is needed to understand and draw conclusions if they are effective in nociceptive and other inflammatory pain syndromes.

NEW DEVELOPMENTS

Research involving cannabis has, by and large, focused on delta-9-THC at the expense of the minimally psychoactive and less well-understood CBD. Recently, efforts have been made to better elucidate the mechanism of CBD and evaluate its utility apart from THC in a wide variety of painful conditions, which has been helped by the 2018 FDA approval of Epidiolex as a treatment of intractable epilepsy and Lennox-Gastaut seizures and a rescheduling of medicinal CBD as a schedule V substance.[66,67]

There is emerging interest in the topical application of CBD in the form of oils and emollients with an associated proliferation of untested products available on the market. A recent trial involving inflammatory skin diseases demonstrated improvement of skin inflammation and scar formation after topical application of CBD.[68] Topical CBD has also been shown to reduce neuropathy-associated pain scores in podiatric patients with peripheral neuropathy in their feet.[69]

One of the primary attributes of CBD is its lack of agonism at CB1, which avoids many of the psychoactive, and therefore adoption-limiting, adverse effects of THC. There is increasing interest in developing synthetic cannabinoids that minimize CB1 agonism.[70] One recent candidate is lenabasum, a synthetic analogue of THC-8 with minimal CB1 agonism and increased selectivity for the CB2 receptor thought to have potent antiinflammatory properties.[71–73] A recent phase II clinical trial of lenabasum as a treatment of systemic sclerosis as well as dermatomyositis was completed and found to have no significant adverse effects, with significant reduction in disease severity and pain.[74,75]

SUMMARY AND FUTURE DIRECTIONS

The heterogeneity of product, different routes of delivery, and wide array of phytocannabinoids make cannabinoids difficult to study. The patchy regulatory framework around cannabis has created a poorly regulated marketplace with little standardization in terms of active ingredients. However, there seems to be a consistent signal demonstrating opioid-sparing effects and modest efficacy regarding the use of cannabinoids in the treatment of neuropathic and cancer-related pain. Early research demonstrates CBD may improve sleep quality and anxiety. More research and RCTs are needed to evaluate the safety and efficacy of cannabinoids as they relate to anxiety, sleep, and pain.

CLINICS CARE POINTS

- Cannabinoids can be useful in treating pain and have been shown to have opioid-sparing properties.
- CBD is not psychoactive and may be useful in treating pain-associated conditions including sleep quality and anxiety.
- Preferentially selecting cannabis products containing a lower THC:CBD ratio reduces undesirable psychoactive side effects and likely improves its efficacy in treating chronic pain.

DISCLOSURE

The authors have nothing to disclose.

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