SPECIAL ARTICLE

Thoughtfully Integrating Cannabis Products Into Chronic Pain Treatment

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Cannabis products (CPs) and cannabis-based medicines (CBMs) are becoming increasingly available and are commonly used for pain management. The growing societal acceptance of cannabis and liberalization of cannabis laws allows patients to access CPs with minimal clinical oversight. While there is mechanistic plausibility that CPs and CBMs may be useful for pain management, the clinical trial literature is limited and does not refute or support the use of CBMs for pain management. Complicating matters, a large and growing body of observational literature shows that many people use CPs for pain management and in place of other medications. However, products and dosing regimens in existing trials are not generalizable to the current cannabis market, making it difficult to compare and reconcile these 2 bodies of literature. Given this complexity, clinicians need clear, pragmatic guidance on how to appropriately educate and work with patients who are using CBMs for pain management. In this review, we narratively synthesize the evidence to enable a clear view of current landscape and provide pragmatic advice for clinicians to use when working with patients. This advice revolves around 3 principles: (1) maintaining the therapeutic alliance; (2) harm reduction and benefit maximization; and (3) pragmatism, principles of patient-centered care, and use of best clinical judgment in the face of uncertainty. Despite the lack of certainty CPs and chronic pain management use, we believe that following these principles can make most of the clinical opportunity presented by discussions around CPs and also enhance the likelihood of clinical benefit from CPs. (Anesth Analg 2024;138:5–15)

GLOSSARY

AE = adverse effect; **AIDS** = acquired immunodeficiency syndrome; **BID** = twice per day; **CB1** = cannabinoid 1; **CB2** = cannabinoid 2; **CBD** = cannabidiol; **CBM** = cannabis-based medicine; **CHS** = cannabinoid hyperemesis syndrome; **CP** = cannabis product; **DC** = District of Columbia; **FDA** = US Food and Drug Administration; **GPR** = G protein-coupled receptor; **IASP** = International Association for the Study of Pain; **THC** = Δ-9-tetrahydrocannabinol; **XR** = extended release

The societal status of *Cannabis sativa* (hereafter, cannabis) is changing dramatically. In 1970, cannabis was criminalized and classified as a schedule I substance, defined as having no therapeutic value and a high potential for abuse.[1] However, 36 states and the District of Columbia (DC) have enacted laws allowing medical cannabis use since 1996, and 17 states and DC decriminalized or legalized adult cannabis use since 2012. Factors contributing to these changes include: (1) increasing acknowledgment of the therapeutic properties of cannabis[1]; (2) growing perceptions of cannabis as minimally harmful[2]; (3) recognition of societal harms (eg, incarceration and trauma)[3] associated with criminalization[4,5]; and (4) the opioid crisis that has highlighted cannabis as an opioid alternative.[6]

In concert with legislative changes, the prevalence of past-year cannabis use among Americans 12 years of age or older increased from 11% in 2002 to 17.5% in 2019.[7] However, the prevalence of past-year cannabis use disorder stayed fairly consistent (~1.8%) in the same time frame.[7] Unsurprisingly, the number of Americans using legal medical cannabis has grown with liberalizing laws, to an estimated 5.5 million people in July 2021.[8] The most common reason for obtaining a medical cannabis license is chronic pain,[9] accounting for nearly two-thirds of qualifying conditions listed in state registries.[10] While state laws require physician authorization for licensure, patients can often obtain authorization through clinical practices specializing in cannabis licensure. Indeed, among medical cannabis patients in Michigan, only 16% reported that the authorizing physician was currently involved in their health care.[11]

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The mismatch between federal and state policies, combined with increasing use disconnected from mainstream medicine, complicates clinical care for patients using cannabis for chronic pain. Minimal formal training is available for physicians, as only 9% of medical schools in the US report offering specific training regarding cannabis use.[12] As such, it is unsurprising that clinicians are often concerned about cannabis-related risks and acknowledge lacking confidence and competence in how to integrate cannabis into clinical practice.[13] In addition to the lack of the training, the cannabis market has provided a multitude of new products that have varied administration routes, formulations, and cannabinoid content (cannabidiol [CBD] and Δ-9-tetrahydrocannabinol [THC]).[14,15] People often use numerous dispensary products[16]—none of which have been approved by the US Food and Drug Administration (FDA).

In this complex environment, pain specialists require straightforward, actionable information to effectively work with patients. Our goal is to narratively synthesize relevant evidence to provide practical advice on cannabis use for chronic pain.

DEFINITIONS

Cannabis-based medicines (CBMs) are pharmaceutical grade products approved for medical use, including synthetic products (eg, dronabinol) and plant-derived products (eg, Epidiolex). See Table 1 for a list of pharmaceutical-grade cannabinoids approved for clinical use. For the purposes of this review, CBMs also include the standardized, research-grade herbal cannabis provided for clinical studies through the National Institute on Drug Abuse-funded facility at the University of Mississippi.

Cannabis products (CPs) are available in state-regulated dispensaries (either medical or adult use) that are not regulated by FDA. CPs include dried cannabis flower (which is typically smoked or vaporized) as well as processed products, such as concentrates, edibles, tinctures, and topicals.

Hemp refers to *C sativa* that contains <0.3% THC, an important legal designation, as hemp products are no longer regulated under the Controlled Substances Act after the passage of the 2018 Farm Bill.[17] As a result, hemp products are widely available in retail outlets and online. As these products are not well regulated, there are concerns about inaccurate labeling for potency, unverified medical claims (prompting FDA "cease and desist" letters), and contamination with heavy metals and other harmful compounds.[18–22]

OVERVIEW OF EFFECT ONSET OF CP ADMINISTRATION ROUTES

The onset and duration of effect vary widely for cannabinoid products.[23] The most commonly used routes of administration are described below, as summarized by MacCallum and Russo 2018.[15] Smoking or vaporizing cannabis flower/concentrates causes effects in 5 to 10 minutes and lasts for 2 to 4 hours. By contrast, oral products such as capsules and edibles take effect in 1 to 3 hours and last for 6 to 8 hours or longer. Sublingual products (eg, tinctures) can be thought of as a pharmacokinetic "middle ground" between inhalation and oral routes with effects generally seen in 15 to 45 minutes and a duration of 6 to 8 hours.[15] However, the effect onset data on sublingual absorption are largely drawn from studies of nabiximols and, thus, may not be consistent with all tincture formulations, which are widely variable and can contain any combination of oils (eg, olive and coconut), ethanol, and other additives. Furthermore, when sublingual products are swallowed, they likely behave in the same way as oral products.[24] Similarly, the effects of topical products are likely quite variable and inconsistent due to the wide variety of formulations, as some are simply suspended in oil[15] and may act locally, while others may contain skin penetrants to enhance transdermal absorption.[25]

CANNABINOIDS

Cannabis contains hundreds of active compounds, including numerous terpenes, flavonoids, and phytocannabinoids (ie, cannabinoids derived from *Cannabis sativa* rather than synthetically produced).[1] While some research is being conducted on some minor

Table 1. Pharmaceutical Grade Cannabinoids

Generic name (brand names)	Active ingredient	Clinical uses	Administration route	Clinically available in United States?
Dronabinol (marinol, syndros, reduvo, and adversa)	Synthetic THC	Approved in United States for postchemotherapy nausea and vomiting, as well as AIDS-induced anorexia	Oral	Yes, schedule II or III depending on formulation
Nabilone (cesamet)	Synthetic THC analog	Approved in United States for postchemotherapy nausea and vomiting, as well as AIDS-induced anorexia	Oral	Yes, schedule II
Nabiximols (sativex)	Plant-derived 1:1 THC:CBD	Treatment of multiple sclerosis symptoms (eg, pain, spasticity, and overactive bladder)	Oromucosal	No (available in many other countries)
Cannabidiol (epidiolex)	Plant-derived CBD	Treatment of seizures in Dravet syndrome and Lennox-Gastaut syndrome	Oral	Yes, descheduled

List of pharmaceutical grade cannabinoid products approved for clinical use in the United States and elsewhere.
Abbreviations: AIDS, acquired immunodeficiency syndrome; CBD, Cannabidiol; THC, Δ-9-tetrahydrocannabinol.

cannabinoids such as cannabigerol and tetrahydrocannabivarin,[26,27] nearly all studies examining phytocannabinoids effects on pain and related symptoms have used CBD and/or THC. THC is considered the primary psychoactive compound in cannabis, and its effects are most commonly associated with the cannabis high, including euphoria, intoxication, and increased appetite.[28] CBD is nonintoxicating and may modulate anxiety and psychoactivity related to THC.[29]

Given that the scientific literature largely focuses on these 2 compounds and that the majority of dispensary products contain THC and/or CBD,[30] we focus on the relevant actions of these 2 compounds in the pain context. Due to the rapid proliferation of literature, we direct the reader to relevant systematic reviews to summarize the current state of the evidence.

EFFECTS OF CBD AND THC ON PAIN—INVESTIGATING DIFFERENT EVIDENCE SOURCES

Preclinical Studies of THC and CBD on Pain

THC is a partial agonist of both the Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) receptors in the endogenous cannabinoid system. For a review on interactions between the endogenous cannabinoid system and pain, please see Woodhams et al 2017[31]. Numerous preclinical studies (reviewed here[32] by the International Association for the Study of Pain [IASP] Presidential Task Force on Cannabis and Cannabinoids) have consistently shown that THC provides significant antinociceptive activity in both injury-related and pathological persistent pain among rats and mice. In contrast with THC, CBD does not bind as a ligand with significant affinity to either CB1 or CB2, instead acting as an allosteric modulator and reverse antagonist of CB1.[33] Some studies have suggested that CBD may exert therapeutic effects through other receptors, including the $5HT_{1A}$ receptor,[34] the transient receptor potential caption channel subfamily V member 1, or G protein-coupled receptors (GPRs) such as GPR55 and GPR119.[32] As with THC, CBD shows similar antinociceptive activity in persistent and injury-related pain among rats and mice.[32] However, translating these results to humans has been challenging due to several factors: (1) legal restrictions on cannabis research; (2) many preclinical studies often use THC or CBD alone rather than whole-plant formulations; (3) biological differences between humans and the animals used in preclinical studies; and (4) the administration routes used in preclinical studies (eg, intraperitoneal injection) are often not comparable to those used in naturalistic or clinical settings (eg, smoking and sublingual).

OVERVIEW OF AVAILABLE CLINICAL TRIALS ON CHRONIC PAIN: DRAWING FROM SYSTEMATIC REVIEWS

Since 2010, >50 systematic reviews and meta-analyses have investigated the clinical trial literature on CBMs for chronic pain.[35] As the most recent systematic review of systematic reviews concluded that most of the published reviews were of poor quality,[35] we refer to the recent, high-quality review published by the IASP Presidential Task Force on Cannabis and Cannabinoids.[36] As with many other systematic reviews of cannabis and pain,[37] this review points out substantial methodological flaws of the CBM clinical trial literature: small sample size, short duration, inconsistent pain measures, heterogeneous, unrepresentative products, very few studies with CBD alone or CBD-dominant products, and the challenges of pooling widely disparate pain conditions into a single analysis.[36] With these caveats, this review reports that there is low- or very low-quality evidence suggesting that CBMs (mostly inhaled cannabis, THC alone, or nabiximols) may provide statistically significant improvement but uncertain clinical benefit in the short term (<4 weeks) for neuropathic pain. CBMs also caused more adverse effects (AEs) than placebo, and the authors cautioned that it was unclear whether benefits outweighed risks. The effects of CBMs for other types of pain, including fibromyalgia, cancer pain, and other chronic noncancer pain conditions, have typically been considered insufficient due to the small number of trials and limited number of participants.

OBSERVATIONAL STUDIES

As conducting clinical trials with schedule I drugs is burdensome and the available study drug is not representative of CPs from dispensaries,[1] many investigators have turned to observational study designs to investigate CP effects on chronic pain.[38] These studies provide a useful foil to the clinical trial literature, as they include many more participants and highlight naturalistic use patterns that have yet to be formally tested. As noted by the former director of the Centers for Disease Control, Thomas Frieden, other data sources beyond clinical trials can be used to inform clinical and public policies.[39] This holds especially true for CPs, as rapidly changing cannabis policy has and likely will continue to outpace clinical trials. We acknowledge that these observational studies are often limited by one or more of the following: (1) selection bias, with participants currently using CPs for pain; (2) lack of control group; (3) cross-sectional study design; and (4) lack of objective measures (eg, urinalysis and CP content).

Despite these caveats, several actionable trends emerge from the observational literature of patients with chronic pain. First, many patients report that CPs are effective for pain,[40–42] and some prefer CPs to many other medication, reporting that they are more effective for managing pain.[40,43–45] Second, some patients either use CPs as a substitute for opioids and

other pain medications or incidentally reduce their use of pain medications after initiating CP use. This trend has been reported in cross-sectional and longitudinal studies in many states throughout the United States,[46–51] as well as Canada[38,52,53] and Israel.[54–56] Recent data also suggest that people may be using hemp-based and CBD-dominant products in this same manner for fibromyalgia.[57,58] Third, people often substitute CPs for other medications for harm-reduction reasons, such as fewer harmful side effects or fewer withdrawal effects.[38,48,52] While studies comparing the effectiveness of CBMs and pain medications are generally lacking, pain medications (especially opioids and benzodiazepines) can cause hazardous side effects, including lethal overdose,[59] which may enhance CP desirability for harm reduction. Fourth, dosing practices and products are dramatically different from the rigidity of clinical trials, with participants utilizing numerous administration routes, CPs with variable CBD and THC contents, various symptoms (eg, sleep, pain, anxiety, and mood), and a wide variety of formulations (eg, olive oil suspensions, cookies, gummies, tinctures, and concentrates).[16,52,60,61] This naturalistic use often occurs with little or no clinician oversight or input, as many clinicians who authorize cannabis use have no further involvement in their health care.[11] Fifth, CPs are often used for medical, recreational, or both medical and recreational reasons,[62] resulting in distinct use characteristics, such as greater use of inhalation routes among people using for recreational purposes and more CBD use among people using solely for medical purposes.[16] Also, many people report using cannabis for medical purposes even if they do not have medical cannabis licenses, exemplified by a survey of n = 1000 patrons at an adult use dispensary, 65% and 74% of whom used CPs for pain and sleep, respectively.[63]

CBMS AND CPS FOR COMMON PAIN-RELATED SYMPTOMS: SLEEP AND ANXIETY

Sleep

Sleep is often disrupted by chronic pain, and pain and sleep are known to have a bidirectional relationship such that decrements in sleep may cause decrements in pain or vise versa.[64] Small clinical trials (n = 17 and n = 73, respectively) have shown that dronabinol may improve obstructive sleep apnea symptoms.[65,66] Similarly, small trials found that nabilone enhances sleep quality among people with fibromyalgia compared to amitriptyline (n = 31)[67] and decreased nightmares compared to placebo in a crossover design among n = 10 people with posttraumatic stress disorder.[68] A secondary analysis of phase I–III clinical trials using nabiximols that drew from >2000 subjects and 1000 patient years of data reported significant sleep improvements among people with multiple sclerosis and neuropathic pain.[69]

While studies investigating the use of CBD alone for sleep are more limited, an open-label clinical trial with CBD (n = 15 subjects) showed that 160 mg of CBD improved total sleep time among people with insomnia,[70] and a large case series (n = 72) reported improvements in sleep quality and sleep disturbance among people with sleep difficulties when using 25 to 75 mg/d of CBD.[71] Straddling the pain/sleep interface, an observational study of n = 97 individuals taking opioids for chronic pain management reported that adding 30 mg of a standardized CBD product for 8 weeks resulted in 53% of participants reducing their opioid consumption as well as statistically significant improvements in pain and sleep scores.[57] However, much remains unknown about best practices for cannabinoid use in sleep settings, as some literature suggests that cannabinoids may improve sleep in the short term but cause decrements in the long term.[72,73]

Anxiety

Among people with chronic pain, comorbid anxiety is associated with worse pain and related symptoms.[74] A recent systematic review of CBM for psychiatric conditions (n = 31 trials and n = 605 participants that investigated anxiety) reported that there was very low-quality evidence that pharmaceutical-grade THC (either alone or combined with CBD) may reduce anxiety symptoms among people with multiple sclerosis, chronic noncancer pain, or other medical conditions.[75] However, these trials were typically small (median of n = 30 patients), and none of these studies had anxiety as a primary outcome, so anxiety may have improved in concert with other symptoms. Furthermore, long-term observational studies have shown associations between cannabis use (especially heavy use) and anxiety[1] as well a greater symptom burden.[76]

In small clinical trials, CBD alone has also been shown to improve anxiety.[77] In a recent, double-blind clinical trial among n = 37 teenagers with social anxiety disorder in Japan, 4 weeks of 300 mg/d of CBD significantly improved social anxiety symptoms and fear of negative evaluation.[77] This range of dose (300–600 mg) of pure CBD has also been shown to reduce anxiety when given acutely before public speaking tasks (sample sizes ranging from n = 24–60).[78–81] Of interest, some studies show an inverted U-shape dose-response curve, with middling doses (300 mg) produced greater anxiolytic effects than higher doses (eg, 900 mg) compared to placebo.[79] Some naturalistic studies show that lower doses of CBD may be anxiolytic as well: eg, psychiatric patients taking 25 to 75 mg of CBD per day reported significantly reduced anxiety in a large, longitudinal case series (n = 72).[71] A recent systematic review on the interplay between CBD and THC also suggested that CBD may reduce anxiety associated with THC intoxication, although findings were not uniform across different studies.[29]

AES, HARMS, AND MEDICATION INTERACTIONS

AEs and Harms

As with any medicine, CBMs and CPs can cause harm. In this context, we note that CBMs and CPs are very unlikely to cause lethal overdose, which is a reason why many people often cite using CPs in place of other pain medications.[82,83] The IASP Presidential Task Force on Cannabis and Cannabinoids systematic review of the safety of CBMs in clinical trials reported that the use of various CBMs (cannabis, oromucosal THC, and oral THC) all increased the risk of nonserious AEs, but not with serious AEs or death.[84] Similarly, the use of CBMs was associated with a higher risk of withdrawal from studies. Observational literature examining safety of CPs among people with chronic pain has similarly concluded that CPs are associated with a higher risk of nonserious AEs, most commonly including dizziness, somnolence, and disorientation.[54,85] However, reports on the safety and tolerability of CPs when used in naturalistic medical contexts remain sparse.

The IASP systematic review also drew from reports of CP use (typically in recreational contexts) to clarify potential risks outside of the clinical trial context.[84] This report highlighted the fact that recreational cannabis use was significantly associated with the risk of psychosis (lifetime risk and onset earlier in life), motor vehicle accidents, respiratory issues (including coughing, bronchitis, and wheezing), and numerous short-term AEs associated with intoxication, including anxiety, tachycardia, dizziness, drowsiness, and nausea/vomiting. These short-term AEs are congruent with those listed in the drug brochures for CBMs, including dronabinol and nabiximols. Clinicians should also be aware of cannabinoid hyperemesis syndrome (CHS), a condition characterized by heavy use of high-dose cannabis and cyclical vomiting.[86] There is some palliation of CHS symptoms with hot baths or showers, which is suspected to be due to interactions known between the cannabinoid system and transient receptor potential V1 receptors that help control thermoregulation.[86] However, the only known effective long-term treatment for CHS is cessation of cannabis use.[86,87] This syndrome has unclear pathophysiology, but some preliminary studies have suggested that genetic factors affecting metabolic processing of THC may play a role in who develops CHS.[88] Overall, as much of the evidence on harms comes from recreational settings and very heavy use, it is uncertain how well they translate to risks of CPs when used for pain management.

Drug-Drug Interactions

THC and CBD are promiscuous compounds that have many potential interactions with different medication classes. The current literature has not fully characterized potential drug-drug interactions, so it remains important to monitor safety among people using CPs or CBMs. We refer readers to the drug labels of FDA-approved Epidiolex (CBD)[89] and dronabinol (THC)[90] for known interaction, which we have summarized in Table 2.

PRAGMATIC CONSIDERATIONS FOR CLINICAL CARE

To summarize the scientific literature, the abundant mechanistic plausibility for cannabinoid analgesia has not translated to general analgesic effectiveness in the current clinical trial literature, which shows small analgesic impacts on neuropathic pain and insufficient data for other types of pain.[36] However, this literature is widely acknowledged to be limited by methodological flaws[37] and legal barriers, which have significantly hindered the conduct of therapeutic cannabis research: both by directly limiting funding and through complex and expensive regulatory requirements that discourage investigators from venturing into this research space.[91] Despite this incomplete evidence base, a growing number of people use CPs

Table 2. THC and CBD Drug-Drug Interactions and Physician Considerations

Cannabinoid	Drug interaction	Medication examples	Physician considerations
CBD or epidiolex	Moderate or strong inhibitors of CYP3A4 or CYP2C19	CYP2C19: fluvoxamine CYP3A4: ketoconazole	Consider dose reduction
	Strong inducers of CYP3A4 or CYP2C19	CYP3A4: phenobarbital CYP2C19: rifampin	Consider dose increase
	Substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19	UGT1A9: propofol UGT2B7: naproxen CYP2C8: repaglinide CYP2C9: celecoxib CYP2C19: diazepam	Consider possible dose reduction
	Substrates of CYP1A2 and CYP2B6	CYP1A2: theophylline CYP2B6: bupropion	Dose adjustment may be necessary
THC or dronabinol	Inhibitors and/or inducers of CYP2C9 and CYP3A4	CYP2C9: sulfaphenoazole CYP3A4: ketoconazole	Monitor patient for potential loss of efficacy
	Highly protein-bound drugs and narrow therapeutic index drugs	Warfarin, cyclosporine, and amphotericin B	Be cautious of use and carefully monitor patients

Drug-drug interactions, dose adjustments, medication examples, and other clinical considerations when taking CBD or THC products.
Abbreviations: CBD, Cannabidiol; THC, Δ-9-tetrahydrocannabinol.

for chronic pain,[10] with many reportedly doing so for reasons of harm reduction.[48,58]

Notwithstanding these uncertainties and complications, we believe that clinicians must prepare to engage with patients using CPs for several reasons. First, failing to do so could harm the therapeutic alliance, as patients may withhold relevant medical information if they feel unfairly judged after disclosing cannabis use. Second, not engaging about CPs can lead to potential harm. For example, we recently showed that nearly 70% of people substituting CPs for prescription medications either had not informed or delayed informing their primary care provider about this substitution,[11] which for some drugs (eg, disease-modifying anti-rheumatic drugs) could be harmful without appropriate clinician oversight. Third, given expanding legalization and decriminalization policies, clinicians cannot realistically prevent patients from using CPs or prevent access to legally available CPs. Patients can likely find another authorizing provider if their primary physician will not authorize their license.[11] Fourth, providing accurate information about appropriate CPs remains essential for patients' health and safety due to reports of CP contamination (eg, pesticides) and inaccurate labeling,[18,21] as well as misleading advertising by dispensaries and CBD companies that promote unverified medical benefits.[22,92] As such, we believe that conversations about cannabis represent a valuable clinical opportunity that physicians can use to focus on 3 mutually reinforcing goals: (1) strengthening the therapeutic alliance; (2) harm reduction and benefit maximization; and (3) using clinical judgment to provide appropriate patient care.

ENHANCING THE THERAPEUTIC ALLIANCE THROUGH BUILDING PARTNERSHIPS AND MUTUAL UNDERSTANDING

Cannabis use remains stigmatized due to criminalization.[93] Several studies report that stigma causes patients to avoid conversations about cannabis for fear of shame, being labeled as a drug addict, or having their decisions invalidated due to heavy-handed concerns about addictions.[45,93–95] However, discussions about medications, including CPs, remain an important part of pain management and represent an important relational space for patients and clinicians to build trust.[96] In a qualitative study of people with fibromyalgia, patients reported feeling disappointment, shame, humiliation, and rejection when physicians expressed lack of knowledge about a certain treatment or offered prescription perceived by patients to be potentially risky.[96] However, physician willingness to trial new medications when patients had poorly managed symptoms was perceived as useful for building an effective patient-clinician partnership. Doing so leverages the unique psychological support clinicians can provide for their patients, which may promote health literacy, empower patients to cooperate in finding the right treatment, enhance symptom relief,[97] and help build adaptive coping skills for symptom management.[98] As such, cultivating knowledge about CPs to build partnership with patients represents a key opportunity to enhance the therapeutic alliance. Beyond fostering trust and open communication, engaging with patients about CPs holds space for patients to share about treatment challenges, successes, and concerns (which may include CPs), setting the stage for conversations regarding harm reduction and benefit maximization.

HARM REDUCTION AND BENEFIT MAXIMIZATION

When assessing use and providing education, clinicians can focus on 4 concepts: (1) routes of administration; (2) titration; (3) cannabinoid content; and (4) use timing. Clinical takeaways are summarized in Table 3.

Routes of administration have widely variable effect onset and length of effect, characteristics that can guide judicious use. As with other drugs with addictive potential, inhalation routes like smoking or vaporizing lead to rapid increases in drug effect[15] and also lead to more likability and thus may increase the dependency risk. Oral or sublingual formulations take effect more slowly but last longer, lowering likeability while also providing long-term symptom coverage. For example, one could use capsules analogously to extended-release medications while using sublingual tinctures for breakthrough pain.[15] However, based on surveys of people using medical cannabis for chronic pain,[16,40,46,50] inhalation remains the most common administration route. Sharing information about these alternative administration routes may help reduce respiratory harms. If a patient insists on inhaling, we suggest vaporizing cannabis flowers to reduce exposure to combusted plant materials.[99] While we and other clinicians believe that oral and sublingual CPs are preferable to inhalation,[15,101,102] we caution that oral products have been associated with higher incidence of hospital visits than inhalation,[103] possibly because edibles are often potent (>50 mg/item),[104,105] are sold as baked goods (eg, brownies), and their delayed onset may tempt people to take a second dose before the first takes effect.

As such, titration is key to judicious use, both to avoid overdose and because the cannabis "high" is often conflated with symptom relief.[15] As demonstrated by a secondary analysis of inhaled cannabis for painful diabetic neuropathy, cannabinoid effects follow an inverted U-shape curve, where higher doses may result in worsened rather than improved symptoms.[106] Thus, it is critical to counsel patients that intoxication is not equivalent to therapeutic benefit, and to "start low and go slow." We suggest starting

Table 3. Methods of Harm Reduction and Benefit Maximization

Domains	Clinical pearls
Administration routes	Use oral routes: tinctures for breakthrough symptoms due to faster onset (analogous to PRN) and capsules for long-lasting effects (analogous to XR).[15] Avoid inhalation if possible. However, vaporizing cannabis is preferable to smoking if using cannabis flowers.[99]
CBD versus THC	THC causes intoxication, analgesia, and sedation. THC cannabis products are only available in states with legal cannabis.[1] CBD is nonintoxicating, a potent anticonvulsant,[100] and causes anxiolytic effects that may reduce THC psychoactivity.[29] Hemp-derived CBD products (<0.3% THC) are descheduled under the Controlled Substances Act and are, thus, widely available.[17]
Dosing and titration	Start low, go slow using CBD or CBD-dominant products to begin. Start with 5–10 mg CBD BID and increase slowly, adding THC (1–2 mg at a time) if CBD preparations are not working.[15] Getting high is not always necessary for pain/symptom relief.[15,101,102]
Timing of use	Use the right medicine at the right time for appropriate symptoms. For example, for trouble falling asleep, use a 1:1 CBD:THC tincture 30 min before bedtime.[15] Avoid use of THC during working hours or while operating a vehicle.[28]

Clinical pearls on how to optimize different domains of cannabis use.
Abbreviations: BID, twice per day; CBD, Cannabidiol; PRN, pro re nata; THC, Δ-9-tetrahydrocannabinol; XR, extended release.

at low doses (5–10 mg CBD and 0.5–3 mg THC) and increasing the doses every few days until medical benefit is maximized while side effects remain minimal.[15,99,107] MacCallum et al[102] recently suggested that patients should use up to 50 mg of CBD before being classified as a potential nonresponder, while considering higher doses if there is suboptimal benefit. Similarly, MacCallum and Russo[15] suggest titrating up to a maximum dose of 30 mg of THC per day and only increasing doses from that point if side effects are not outweighing benefits. This slow, methodical process of dosing cannabis has long been known, with the 1932 Dispensatory of the United States stating: "One of the great hindrances to the wider use of this drug is the great variability in the potency of different samples of cannabis which renders it impossible to approximate the proper dose of any individual sample except by clinical trial … The only way of determining the dose of an individual preparation is to give it in ascending quantities until some effect is produced."[108] This largely holds true today amid the CPs available in state-licensed dispensaries.

In concert with titration, skillful use of products based on cannabinoid content will help optimize outcomes and protect patients. Some patients may not wish to use THC to avoid intoxication or because they have had a bad experience with cannabis in the past. For such individuals, CBD-dominant products are preferable. Using CBD-dominant products during work hours or while driving reduces risks associated with THC-related functional impairments. However, THC is likely helpful for some people, both for pain and also for sleep difficulties.[1] Using THC products at home or in the evening may be more appropriate for many individuals to avoid intoxication on the job and enhance sleep. Finally, while more research is needed to fully elucidate the interplay between CBD and THC, the potential enhancement of THC analgesia of CBD[109] and mitigation of some of the negative side effects of THC (including anxiety)[29] make co-use of these compounds an attractive alternative to THC alone.

Finally, timing brings together patient needs and self-knowledge of symptoms with the other 3 concepts listed. Synchronizing dosing with the patient's most pressing symptoms may reduce unnecessary use while providing a targeted medical effect. For instance, many people with chronic pain also have sleep difficulties that worsen pain[110] and may be smoking or vaporizing cannabis 5 or more times per day, 7 days per week.[111] However, smoking may not help a patient stay asleep, as the effects only last 2 to 4 hours and also causes respiratory harm. Counseling this patient to reduce their inhalation during the day and to take an oral or sublingual THC product before would produce a longer lasting effect and provide more targeted symptom relief.[15]

With sufficient education about these concepts, clinicians can then apply practical judgment and patient-specific knowledge for shared decision-making.

APPLYING CLINICAL JUDGMENT AND PRINCIPLES OF PATIENT-CENTERED CARE

Patient-centered care has been increasingly recognized as a key component of clinical care.[112] This paradigm focuses on patient needs and preferences within their own unique context, including what outcomes are considered most meaningful. While assuming this lens in the context of CP may pose some unique challenges (eg, stigma), these challenges do not change the fundamental nature of using CPs: just like other pain medications, these products may provide relief for some people, while in others, the risks may outweigh any potential benefits.[113] To quote Nutt et al,[114] individual trials are "the core of medical practice since every time a medicine is prescribed an n = 1 experiment is being conducted." Thus, the job of the clinician is to ensure that n = 1 trials with CPs are thoughtfully conducted, using the practices described above as well as drawing from treatment plans used for decision-making

around other medications with abuse potential, such as opioids.[115] This includes developing shared definitions of treatment success and failure, tracking symptoms with mutually agreed-on measures (eg, pain and sleep), when to escalate doses, identifying potential drug-drug interactions, and navigating changed medication use that may result during CP therapy.[116] To this last point, many aforementioned surveys show interest in using CPs as substitutes for pain medications—especially opioids—due to associated harms. We thus refer readers to the proposed recommendations for tapering outlined by Sihota et al.[107] This guidance drew from a panel of researchers and physicians with expertise on cannabis and pain and used a Modified Delphi process to create consensus guidance on using cannabinoids in the presence of opioids, tapering opioids during use of cannabinoids, and monitoring patient safety and outcomes.

DIRECTIONS FOR FUTURE RESEARCH

Future studies should include a breadth of rigorous study designs to more holistically evaluate CP impacts on pain. Clinical trials clearly remain the gold standard of evidence, especially if they use products representative of available CPs.[117,118] However, cannabis remains schedule I, which adds many roadblocks to swiftly conducting clinical trials.[91] Thus, until definitive trials are available, we recommend drawing from complementary studies that utilize real-world data, including: (1) prospective longitudinal or registry studies, which are already ongoing in some states (eg, Florida[119] and Minnesota[120]) or countries (eg, United Kingdom[121] and Israel[54]) with medical cannabis programs; (2) longitudinal studies partnering with companies whose mobile apps assess outcomes of specific medical CPs available in state-regulated dispensaries[41,42]; (3) retrospective chart review or case series studies among people who use standardized cannabinoid products[71,122]; and (4) pragmatic trials that empirically assess the dosing regimens[101] proposed in the current scientific literature. These short-term research efforts would be aided by medical systems, including standardized assessments of CPs into electronic data capture, and would also inform study designs for future clinical trials.

CONCLUSIONS

The clinical trial literature on CPs and CBMs for chronic pain management is inadequate to provide the same kind of clinical structure and prescription medicine model used for other medications. However, given recent trends in cannabis liberalization, clinicians cannot wait years for definitive clinical trials before engaging with patients about these products. Instead, clinicians can better serve their patients by focusing on maintaining and strengthening the therapeutic alliance with patients using cannabis, harm reduction, and applying pragmatic clinical judgment complemented by the latest scientific literature. ■

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