Cannabis and Pain Management

Fred Rottnek, MD, Sheryl Lyss, MD, John Hartman, Geoffrey Panjeton, MD, and Amanda Hilmer, MD

Family physicians are fielding questions about cannabis –particularly for the use of cannabis for treatment of pain. Like about every substance ingested to treat medical conditions, cannabis has risks and benefits. But regarding evidence-based practice and practice-based recommendations for patients about cannabis use, the cart is in front of the horse. Cannabis use is still illegal at a federal level and a Schedule 1 drug, but most states have challenged federal law by decriminalizing or legalizing cannabis for a variety of uses. Research is difficult due to this federal status as a Schedule 1 drug since federal funding is not readily available to support research. As a result, physicians have little to no guidance about the clinical usefulness of the product. This article explores what we know and what we are learning about cannabis, and the authors provide clinical guidance for patient care based on this evidence. (J Am Board Fam Med 2024;37:784–789.)

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Introduction

Family physicians are fielding questions about cannabis—particularly for the use of cannabis for treatment of pain. This common plant is also the most used federally illegal drug.[1] Like about every substance ingested to treat medical conditions, cannabis has risks and benefits. But regarding evidence-based practice and practice-based recommendations for patients about cannabis use, the cart is in front of the horse. Marketing and availability of cannabis products have outpaced data about their safety and efficacy. There are prolific marketing messages of cannabis being safe as a natural product, but there is also great variability in state laws that maintain the illegality of cannabis for any use due to the potential for adverse events. Cannabis use is still illegal at a federal level and a Schedule 1 drug, but most states have challenged federal law by decriminalizing or legalizing cannabis for a variety of uses. Research is difficult due to this federal status as a Schedule 1 drug because federal funding is not readily available to support research. As a result, physicians have little to no guidance about the clinical usefulness of the product. This article explores what we know and what we are learning about cannabis, and the authors provide clinical guidance for patient care based on this evidence.

Cannabis Forms and Routes of Use

Cannabis contains more than 100 different cannabinoids, but the 3 most well-known are tetrahydrocannabinol (THC), cannabidiol (CBD), and terpenes.[2] If a cannabis plant contains 0.3% or more THC, the product has been called marijuana, although now the use of the term marijuana is controversial due to associations of the term with racism and criminalization.[3] THC is the psychoactive compound that is responsible for the "high" associated with cannabis use. (If the THC level is less than 0.3%, the product is hemp. Hemp has no restriction on growth in the US.) The Agricultural Improvement Act of 2018 removed hemp and hemp products from the Drug Enforcement Administration's schedule of controlled substances.[4] CBD products are extracted from hemp and are legal to grow and sell. CBD

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Corresponding author: Fred Rottnek, MD, 1008 South Spring Street, #3208, SSM Health SLUCare Academic Pavilion, St. Louis, MO 63110 (E-mail: Fred.Rottnek@health.slu.edu).

has little-to-no psychoactive effects and is thought to have anti-inflammatory and pain-relieving properties. Terpenes are aromatic products that share some properties with CBD, but they also have promising antibacterial, antifungal, and anticancer properties.[5]

Cannabis can be smoked as joints (hand-rolled cigarettes), blunts (emptied cigars or cigarettes that have been partly or completely refilled with cannabis), or in pipes or water pipes (bongs). Individuals can also vape, or use electronic delivery systems, in which THC is dissolved in a volatile solution, heated, and inhaled. Edible products are available as brownies, cookies, or candy, or brewed as a beverage. A method of ingesting high-potency THC is smoking or eating different forms of highly concentrated THC resins, sometimes called oils, budder, wax, or shatter.[6]

Cannabis and Pain: What Do We Know? What Is in the Literature?

Cannabis has been used for centuries to treat pain. To provide, practical information for family physicians, the authors reviewed the published literature since 2015 for meta-analyses and systematic reviews of randomized controlled trials of cannabis for analgesia; studies focusing on cancer and terminal illness pain were excluded. The 12 reviews that met these criteria examined conditions such as neuropathic, rheumatological, other noncancer chronic pain, acute and peri-operative pain, and experimental pain. The literature review for this article was conducted similar to a systematic review-style research on the topic of cannabis and pain. The PRISMA algorithm was employed to organize and attempt to standardized exclusion and inclusion of articles. In order to understand the body of research on cannabis and pain, only systematic reviews, meta-analyses, and randomized controlled studies were included. Due to the wide array of pain etiologies, disorders with unique pain schema were not included. These disorders/diseases that were excluded are cancer, cirrhosis, terminal illness and palliative care, psychological illness, and pediatric pain. The search engine was PubMed. Then 195 studies were selected to be reviewed based on their titles (addressing both cannabis and pain). Based on 195 studies, all of the abstracts were read. This further winnowed down the results to 120. THC and CBD are the most abundant and well-studied of the cannabinoids (phytochemicals in the marijuana flower or bud). Studies looking at CBD, THC, or both were included despite that both compounds are metabolized in different ways and may have differing effects on pain. All studies included had an experimental design. This was in order to understand the routes of administration in a clearer way, with experimentally rather than user reported. Based on the studies reviewed, categories was chosen from this search (10 articles) that included topics most relevant to family physicians.

Neuropathic Pain

Neuropathic pain is a subset of chronic pain that results from a wide variety of conditions such as multiple sclerosis, diabetic neuropathy, alcoholism, and nerve injury. One meta-analysis found that low-dose inhaled cannabis can provide short term relief for 1 in 5 to 6 patients with neuropathic pain (number needed to treat, 5.6).[7] Pooled data of 16 studies on neuropathic pain demonstrated that cannabis was associated with a 30% decrease in pain severity. However, the research group considered these data to be low quality evidence.[8]

Rheumatological Pain

Authors of a systematic review of cannabis for treatment of rheumatologic pain identified only 4 small studies of patients with rheumatoid arthritis, fibromyalgia, and osteoarthritis and concluded that there is low-quality evidence that pharmaceutical cannabis might be associated with improvements in pain in patients with rheumatoid arthritis and fibromyalgia.[9]

Other Non-Cancer Chronic Pain

There is moderate quality evidence that cannabis—smoked cannabis, oromucosal cannabis sprays, and oral cannabinoids—has a small effect in treating chronic, noncancer pain compared with placebo at time points up to 6 months; although oral cannabis had a larger relative reduction in pain than oromucosal or smoked cannabis, the difference was not statistically significant.[10,11]

Acute and Post-Operative Pain

The use of cannabinoids for acute and perioperative pain management is not well-supported in the literature. A 2020 meta-analysis assessing cannabis use in acute postoperative pain found no difference in

pain levels or opioid use compared with controls. Although, there are some signals that indicate a possible analgesic and opioid sparing effect in the perioperative period with some cannabinoid products, many studies indicate no effect, worsening pain and challenging side effects such as sedation and hypotension.[12]

Experimental Pain

In the setting of experimental pain (pain stimulus provided by study designers), cannabis administration was associated with a minor increase in pain threshold, meaning that a greater pain stimulus was required to induce pain, but did not reduce the intensity of ongoing experimental pain. However, cannabis was associated with small-to medium-sized reductions in the perceived unpleasantness of pain, suggesting that cannabis may modulate the affective processes of pain.[13] A review of evidence for cannabis in the treatment of chronic, noncancer pain, focusing on quantitative sensory testing in a systematic review of 39 studies found inconsistent evidence to support cannabis as a mediator of experimental pain.[14]

Adverse Effects of Cannabis Used to Treat Pain

Johal et al. reviewed 35 studies with data on adverse events found an increased risk of mild or moderate adverse effects with cannabis (48%) compared with placebo (40%); serious adverse events were rare in both the cannabis and placebo groups (Johal et al., 2020).[10] The most frequent side effects were dizziness (31%), application site discomfort (18%), asthenia (16%); fatigue (15%), increased appetite (15%), dry mouth (14%), drowsiness (14%), nausea (13%), and hallucinations (13%). Long-term side effects could not be evaluated given the short durations of the included studies. Another study found higher levels of dizziness and hypotension in patients receiving cannabis compared with those who received placebo. The majority of included reviews reported frequent mild adverse effects; serious adverse effects were rare.

Methodologic Limitations

There are many limitations of the current body of literature on cannabis and pain including short timelines (most under 6 months, many less than 1 month) and small sample sizes. Almost all RCTs compared cannabis with placebo rather than with common analgesics used for chronic pain such as NSAIDs or acetaminophen which limits usefulness for practitioners and patients in evaluating options for treatment of pain. Because of the heterogeneity of cannabis products (including different cannabinoids and lack of consistent THC:CBD ratios), dose, and routes of administration, findings from particular studies cannot be generalized to medical cannabis. Taken together, these studies demonstrate a lack of consistency in both method and outcome but suggest that cannabis has the potential to provide a small benefit relative to placebo in treating pain. The most promising aspect of the literature was for neuropathic pain, where there is weak but emerging evidence for potential benefit of cannabis. Most reviewers conclude that, at this time, evidence is insufficient to recommend cannabis to treat pain because the level of evidence for its benefit is not strong and adverse effects of cannabis are frequent.

Additional Emerging Cautions with Cannabis Use

Family physicians are at the front lines when patients present for complications of cannabis use.

Acute adverse effects of cannabis use include dizziness, drowsiness, nausea, increased heart rate, hyperemesis, psychomotor impairment, and increased risk of motor vehicle accidents.[15] Long-term adverse effects of smoking marijuana include cannabinoid hyperemesis syndrome, and psychosis.[16] Concerns are escalated for adolescents and young adults, particularly those engaging in regular, high potency cannabis use. Several studies are teasing apart whether associated effects on learning and risk of lowering thresholds for psychotic episodes and earlier appearance of schizophrenia are correlative or causative.[17,18]

Cannabinoid Hyperemesis Syndrome (CHS) consists of severe recurrent nausea and vomiting in

Table 1. Enzymes Inhibited by THC and CBD

Substance	Enzymes Inhibited
THC	CYP3A4, CYP2D6
CBD	CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A9, and UGT2B7

Abbreviations: THC, tetrahydrocannabinol; CBD, cannabidiol.

Table 2. Practice Recommendations

Recommendation	Grade
Discuss known risks and benefits, evidence, safety concerns, and side effects of cannabis use	A
Screen all pre-surgical patients for the amount and frequency of their cannabis use, type of cannabis product, time of last consumption, and route of administration	A
Postpone procedure involving sedation if a patient experiences acute cannabis toxicity and has impairment in their decision-making capacity	A
Educate patients inquiring about cannabis use that there is weak but emerging evidence that cannabis can treat central pain caused by neuropathic pain as an adjunctive or third line treatment	B
Review and update patient medication lists when patients inquire about use of cannabis	C

patients with prolonged chronic use of cannabis (more than weekly use), which typically presents in 3 phases. The prodromal phase consists of morning nausea, abdominal discomfort, and fear of vomiting. It may last months or years.[19] The second or hyperemetic phase consists of severe, intense emesis with vomiting episodes throughout the day. Patients may present to emergency departments repeatedly, but their lab testing and imaging are often nonspecific. Weight loss may occur in this phase, which may continue for 24 to 48 hours. Relief is associated with hot-water bathing.[20] For patients to enter the recovery phase, complete cessation of cannabis use is required; This phase may take months while lipophilic cannabinoids are eliminated from the patient's system.[21]

Medication Interactions with Cannabis

Family physicians also must remain vigilant about emerging data regarding drug interactives with cannabis. One tool useful for identify drug interactions, as well as preparing patients for surgical and other procedures requiring sedation is the American Society of Regional Anesthesia and Pain Medicine's recently released consensus guidelines to assist in caring for patients who use cannabis/cannabinoid medications.[22]

There are several potential interactions between THC and CBD and other medications, including those with similar psychoactive effects such as central nervous system depressants, benzodiazepines, opioids, alcohol, and antihistamines, which may result in increased sedation. In addition, coadministration of cannabis with tricyclic stimulants, sympathomimetics, and antidepressants may cause tachycardia. THC is metabolized by the CYP3A4 and CYP2C9 enzymes, whereas the metabolism of CBD involves the CYP3A4 and CYP2C19 enzymes. Table 1 outlines the various enzymes that are inhibited by THC and CBD. Coadministration of medications that involve these enzymes may affect THC and CBD or medication plasma levels.

The guidelines also highlight the potential for interactions between anticoagulant and antiplatelet medications with THC and CBD. Patients may be at risk for increased bleeding due to inhibition of CYP enzymes and P-glycoproteins resulting in increased levels of warfarin, direct-acting oral anticoagulants (DOACs), and clopidogrel. Other notable interactions include substrates of the CYP2D6 enzyme, which includes several opioids, antidepressants, antipsychotics, antiarrhythmic and β blocker medications. THC and CBD inhibition of CYP enzymes can result in increased drug levels. CBD may also cause increased levels of nonopioid analgesics (acetaminophen, NSAIDs) and propofol due to interactions with the UGT1A9 enzyme.

Beyond medication interactions, CBD and THC consumption can have a variety of impacts on a patient's ability to tolerate sedation and anesthesia. The guidelines recommend universal screening for amount and frequency of cannabis use, type of cannabis product, time of last consumption, and route of administration (Grade A). In addition, procedures should be postponed if the patient experiences acute cannabis toxicity and has impairment in their decision making capacity (Grade A). The guidelines also recommend delaying elective surgery for 1 to 2 hours after acute cannabis smoking due to the potential increased risk of myocardial infarction (Grade C). Family physicians should educate their patients to share their cannabis use with their surgeons and anesthesiologists to minimize potential adverse outcomes.

Conclusion: So, What Do We Tell Our Patients?

Although we are learning much about cannabis and potential therapeutic roles of this plant, physicians should discuss risks and benefits of what is known and what we are learning.

The US literature on the efficacy of cannabis use for pain is scant. There are no published standards of therapeutic benefit of cannabis, such as number

needed to treat. And much of the literature on the topic is limited by lack of consistency. Until we have better practice guidelines from scientific studies, we can still share possible promising practices. And we can certainly share ways to reduce harm—from abstinence to reducing risk according where a product is obtained and how it is consumed.

So, what medical advice can family physicians give in today's world of mixed messages about medical-use cannabis and recreational/adult-use cannabis?

- Avoid early age initiation of cannabis use (i.e., definitively before the age of 16 years),
- Choose low-potency tetrahydrocannabinol (THC) or balanced THC-to-cannabidiol (CBD)–ratio cannabis products,
- Abstain from using synthetic cannabinoids,
- Avoid combusted cannabis inhalation and give preference to nonsmoking use methods,
- Avoid deep or other risky inhalation practices,
- Avoid high-frequency (e.g., daily or near-daily) cannabis use,
- Abstain from cannabis-impaired driving,
- Educate patients that some individuals have a higher risk for cannabis use–related health problems and should avoid use altogether. These include individuals with a personal or family history of schizophrenia, uncontrolled hypertension/coronary artery disease, chronic obstructive pulmonary disease or lung pathology (particularly with smoking and vaping), current immune treatment, and pregnancy

Until the Schedule 1 status of cannabis changes, researchers in the US will remain limited on the ability to conduct randomized, placebo-controlled, blinded, prospective studies, just as we do with the majority of products we call medications in the US. Until then, family physicians can educate patients and families on what we know, what we are learning, and how we can reduce harm around cannabis use.

To see this article online, please go to: http://jabfm.org/content/37/4/784.full.

References

1. CDC. Data and Statistics. CDC. Published 2019. Available at: https://www.cdc.gov/Marijuana/Data-Statistics.htm.
2. National Center for Complementary and Integrative Health. Cannabis (marijuana) and cannabinoids: what you need to know. NCCIH. Published November 2019. Available at: https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know.
3. Thompson M. NPR choice page. Npr.org. Published 2019. Available at: https://www.npr.org/sections/codeswitch/2013/07/14/201981025/the-mysterious-history-of-marijuana.
4. U.S. Department of Agriculture. Hemp. www.usda.gov. Available at: https://www.usda.gov/topics/hemp#:~:text=The%20Agriculture%20Improvement%20Act%20of%202018%20(2018%20Farm%20Bill)%20authorized.
5. Booth J, Bohlmann KJ. Terpenes in cannabis sativa – from plant genome to humans. Plant Sci 2019; 284:67–72.
6. NIDA Cannabis (Marijuana) DrugFacts. National Institute on Drug Abuse. Published December 24, 2019. Available at: https://nida.nih.gov/publications/drugfacts/cannabis-marijuana#mjextracts.
7. Andreae MH, Carter GM, Shaparin N, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. J Pain 2015;16:1221–32.
8. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018;3:CD012182.
9. Fitzcharles M-A, Ste-Marie PA, Häuser W, et al. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: a systematic review of randomized controlled trials. Arthritis Care Res (Hoboken) 2016;68:681–8.
10. Johal H, Devji T, Chang Y, Simone J, Vannabouathong C, Bhandari M. Cannabinoids in chronic non-cancer pain: a systematic review and meta-analysis. Clin Med Insights Arthritis Musculoskelet Disord 2020; 13: 1179544120906461.
11. Yanes JA, McKinnell ZE, Reid MA, et al. Effects of cannabinoid administration for pain: a meta-analysis and meta-regression. Exp Clin Psychopharmacol 2019;27:370–82.
12. Gazendam A, Nucci N, Gouveia K, Abdel Khalik H, Rubinger L, Johal H. Cannabinoids in the management of acute pain: a systematic review and meta-analysis. Cannabis Cannabinoid Res 2020;5:290–7.
13. De Vita MJ, Moskal D, Maisto SA, Ansell EB. Association of cannabinoid administration with experimental pain in healthy adults: a systematic review and meta-analysis. JAMA Psychiatry 2018;75:1118–27.
14. Mun CJ, Letzen JE, Peters EN, et al. Cannabinoid effects on responses to quantitative sensory testing among individuals with and without clinical pain: a systematic review. Pain 2020; 161:244–60.
15. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction 2015;110:19–35.
16. Bui QM, Simpson S, Nordstrom K. Psychiatric and medical management of marijuana intoxication in

the emergency department. West J Emerg Med 2015; 16:414–7.

17. Urits I, Gress K, Charipova K, et al. Cannabis use and its association with psychological disorders. Psychopharmacol Bull 2020 ;50:56–67.
18. Crawford P, Go KV. Schizophrenia. Am Fam Physician 2022;106:388–96.
19. Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev 2011;4:241–9.
20. Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev 2011; 4:241–9.
21. Rella JG. Recreational cannabis use: pleasures and pitfalls. Cleve Clin J Med 2015;82:765–72.
22. Shah S, Schwenk ES, Sondekoppam RV, et al. ASRA pain medicine consensus guidelines on the management of the perioperative patient on cannabis and cannabinoids. Reg Anesth Pain Med 2023;48:97–117.