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Current Concepts

From Flower to Function: Medical Cannabis Modalities in Orthopedic Practice

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Medical cannabis (MC) is a potential therapeutic option for managing several chronic pain and cancer-related symptoms, as well as multiple sclerosis-related spasticity. Despite increasing acceptance and availability in the United States, significant knowledge gaps remain regarding its modalities, pharmacokinetics, and indications, which present a barrier to use for both clinicians and patients. MC is of particular interest within orthopedics, given the prevalence of chronic musculoskeletal pain and acute postoperative pain following surgical procedures. Evidence suggests that MC can alleviate these conditions and reduce opioid consumption, revealing it as a potentially valuable adjunctive therapy within a multimodal pain management regimen that addresses larger public health concerns brought about by the ongoing opioid crisis, characterized by growing opioid misuse and overdose. Federal and state regulations governing MC use and distribution remain complex and variable, however, creating practical challenges for both orthopedic surgeons and patients. This Current Concepts narrative review aims to synthesize the current evidence on MC's various modalities and pharmacologic properties, with a focus on its specific applications in orthopedic care. The review also aims to clarify the regulatory considerations that orthopedic surgeons must navigate when counseling patients and integrating MC into management plans.

INTRODUCTION

Medical cannabis (MC) and its derivatives, cannabinoids, have been used throughout history, with records dating back to ancient China, India, Egypt, and Greece.[1] However, there has historically been stringent regulation in the United States (U.S.), including the Marihuana Tax Act of 1937 and the Controlled Substances Act of 1970, with the latter designating MC as Schedule I, thereby preventing its medical use.[1-3] Despite the past restrictions in the U.S., there has recently been increased interest in MC and cannabinoids due to their potential therapeutic effects. Since the 1980s, when the Food and Drug Administration (FDA) approved the synthetic cannabinoid dronabinol, forty states, three territories, and the District of Columbia now allow the use of MC, with state-specific restrictions.[2-4]

Following MC's increasing acceptance, research has shown its efficacy in the management of chronic pain, chemotherapy-induced nausea and vomiting, spasticity with multiple sclerosis (MS), and human immunodeficiency virus (HIV)-related neuropathic pain symptoms.[3,5-9] While MC has broad applications, its role in orthopedic surgery is of particular interest. Orthopedic patients frequently experience acute postoperative pain and chronic musculoskeletal pain. Given the significant contribution of orthopedic surgeons to national opioid prescribing practices, MC offers a potential adjunct that could reduce reliance on opioids while providing effective analgesia. This Current Concepts narrative review aims to summarize the administration routes, pharmacology, and common indications of MC, while discussing its relevance to orthopedic practice and treating musculoskeletal pain. This review will also describe the evolving regulatory and prescribing considerations most pertinent to surgeons.

TETRAHYDROCANNABINOL AND CANNABIDIOL COMPOSITIONS

MCs can be classified based on their chemical composition and distinct formulations. Clinically, the most relevant and

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recognized therapeutic cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD).[10-13] Other cannabinoids, such as tetrahydrocannabivarin (THCV), cannabigerol (CBG), cannabichromene (CBC), and cannabinol (CBN), are lesser studied but may also exert pharmacological effects.[10-13]

THC is the principal psychoactive component of cannabis, exerting its effects by acting as a partial agonist at endocannabinoid type 1 (CB1) and type 2 (CB2) receptors in the central nervous system, leading to cognitive impairment and feelings of euphoria.[14] CBD, the principal non-intoxicating cannabinoid, modulates endocannabinoid signaling primarily through negative allosteric effects at CB1 receptors and antagonism at CB2 receptors, influencing inflammation and nociception.[13,15-18] In contrast to THC, CBD is not known to produce potent adverse cognitive effects. THC and CBD can both be used independently as therapeutics, but MC can have varying ratios of both components, including high-THC, balanced THC/CBD, and high-CBD/low-THC.[19] There may also be a synergistic or interactive dynamic between these two cannabinoids,[20,21] with CBD potentially being able to reduce the cognitive and psychotropic effects associated with THC.[22] However, these findings are still inconsistently defined and may depend on the specific dose and administration method, requiring further investigation.[20-22]

INHALATION ADMINISTRATION (SMOKING AND VAPORIZATION)

Inhalation is the most common route of MC administration and includes smoking or vaporization. When cannabis is inhaled, the cannabinoids are absorbed into the bloodstream through the pulmonary alveoli in the lungs. This method results in a rapid onset of analgesic effects and a peak concentration within 15 minutes of inhalation.[19,23-26] However, the specific absorption and bioavailability of cannabinoids will depend on inhalation depth, duration, and THC or CBD content.[26] Smoked MC involves inhaling the combusted smoke of dried cannabis flower through cigarettes, pipes, bongs, or other similar devices. Vaporization, or vaping, which involves heating cannabis flower or oils to produce an aerosol or gas, is an alternative that avoids the combustion products and has been quickly growing as a means of risk-reduction.[23,27] However, both chronic vaping and smoking can cause airway irritation, symptoms of bronchitis, and long-term lung function deficiencies.[28,29]

Inhaled cannabis is used for a wide range of indications that reflect its uniquely rapid speed of action. Smoked and vaped MC products are primarily used for pain syndromes where the immediate onset of effects is desirable, including chronic and neuropathic pain. In meta-analyses and randomized controlled trials of patients with neuropathic and chronic pain, inhaled cannabis was found to provide significant short-term relief with a tolerable safety profile.[7,8,30,31] In the oncologic setting, patients have also reported high usage of inhaled MC and relief in several cancer and treatment-related symptoms.[32,33] Despite these findings, the analgesic and therapeutic effects of MC will differ across conditions, and further research is needed to confirm these results. Given the inhaled nature of this modality, physicians and patients should also weigh the potential benefits and risks, especially for patients at increased risk of respiratory complications.[27-29]

ORAL ADMINISTRATION (CAPSULE, SPRAYS/TINCTURES, EDIBLE GUMMIES)

MC can also be ingested. The most commonly available encapsulated cannabis products include hemp seed capsules, dronabinol, and nabilone. Compared to inhalation, the onset of effects for oral methods is more prolonged and may depend on concurrent or past food intake.[34] Despite this variability, the onset is typically 30 minutes to one and a half hours after ingestion, with the concentration peaking around two to four hours and lasting upwards of five hours.[19,23-26] These delayed effects are in part due to the poor gastrointestinal absorption and hepatic first-pass metabolism, which can significantly reduce the bioavailability.[34] The indications for capsule cannabis are evolving and broad. Hemp-derived CBD capsules have been shown to significantly improve chronic musculoskeletal symptoms and quality-of-life measures, such as low back pain from lumbar spine stenosis.[35] According to the American Society of Clinical Oncology, oral cannabinoids such as dronabinol, nabilone, and quality-controlled 1:1 THC:CBD extracts may be potentially useful as adjuncts alongside guideline-concordant antiemetics for refractory nausea and vomiting in patients with cancer.[3]

The oromucosal administration method involves the vascularized buccal and sublingual surfaces of the oral mucosa. Oromucosal formulations most commonly include sprays, tinctures, and dissolvable capsules or tablets.[23] Sprays, including nabiximols (Sativex®), are metered-dose medications applied as an aerosol.[36] Tinctures and drops are liquid-based cannabis extracts applied to the underside of the tongue, and dissolvable tablets are placed under the tongue for disintegration.[37] The mechanism of action of these drugs is to allow the cannabinoids to enter the systemic circulation directly through the highly vascularized sublingual and buccal mucosa in the mouth.[37-40] This method of administration, similar to inhalation, avoids poor gastric absorption and hepatic first-pass metabolism, offering higher THC and CBD bioavailability and a quicker therapeutic onset compared to ingested formulations.[37-40] However, the specific absorption can still vary depending on other factors, like drug composition, saliva pH and flow, and the permeability of the mucosal vasculature.[37-40] The main indications for these formulations are chronic pain and MS spasticity. Evidence has shown that nabiximols and sprays, when used as an adjunct, can significantly improve chronic pain and spasticity-related symptoms, including muscle spasms, fatigue, and sleep quality, with minimal physical and cognitive adverse effects.[36,41,42] However, more research is still needed to confirm long-term efficacy and safety.

MC edibles are THC and CBD products in a chewable form. They are an alternative to traditional inhalation, oral,

or oromucosal formulations. Once cannabis edibles are ingested, the cannabinoids are absorbed through the gastrointestinal tract, which contributes to a delayed onset of effects due to poor gastric absorption, degradation, and hepatic metabolism.[34] Edibles are available in a wide range of THC and CBD concentrations and thus can have significant variabilities in dosing and labeling, especially in the unregulated and commercial market.[43,44] Furthermore, the concentration of THC or CBD in edible products may be unsuitable for medical use.[44] A recent study conducted by Khak et al[45] further confirmed inconsistencies in dosing, with 46.5% and 47.2% of respondents being unaware of their exact THC or CBD dosage, respectively, which raises concerns about the regulation and patient education regarding these MC formulations. Although not FDA-approved, patients continue to use edibles for chronic pain. More research is needed to confirm their analgesic efficacy and to justify broader clinical use.

TOPICAL ADMINISTRATION (CREAMS, LOTIONS, OINTMENTS, GELS)

Topical formulations, such as creams, lotions, ointments, or gels that contain cannabinoids, can be applied directly to the skin.[23,46,47] These medications contain THC and CBD extracted into vehicles designed to permeate the skin barrier and exert the therapeutic effects. Given their topical nature, these formulations offer more targeted relief than inhalation or oral methods. The main benefit of topical administration is delivering cannabinoids directly to affected areas, such as the skin, joints, or peripheral nerves. Thus, they are designed for local action and have limited systemic absorption, lowering the risk of central nervous system side effects such as euphoria or cognitive intoxication.[46-49] The topical delivery of medicinal cannabis also avoids hepatic metabolism and poor gastrointestinal absorption, preserving bioavailability.[47,48]

The main indications for topical MC would be localized musculoskeletal pain and dermatologic conditions. Current research into the use of topical CBD for hand arthritis has indicated a favorable safety profile with significant improvements in pain and disability.[50] Studies have also shown that topical and transdermal cannabinoids can improve pain and function for musculoskeletal and rheumatic conditions, including osteoarthritis.[45,51,52] However, topical cannabinoids are not limited to joint pain, as they have also shown promise in treating certain skin condition symptoms. Research indicates that topical cannabinoids can improve acne and pruritus, as well as erythema and scaling, in atopic dermatitis, contact dermatitis, and psoriasis.[53-55] Nanoformulated forms of CBD, such as emulsions, cryogels, lipid nanoparticles, and nanomicelles, were also identified to potentially offer improved skin delivery and enhanced efficacy for treating various skin conditions.[56] Despite these promising findings, the current landscape of evidence is still growing, and future research should investigate whether topical MC can serve as a viable adjunct or alternative to traditional therapies in musculoskeletal and dermatologic contexts.

MC IN ORTHOPEDIC CONDITIONS

While MC has demonstrated efficacy in managing symptoms across a range of conditions, its role within orthopedics and postoperative pain is paramount. Orthopedic patients frequently experience both acute and chronic pain, and the current treatment paradigms rely on opioids, which can carry significant adverse effects.[57] MC is a potential alternative that can effectively provide analgesia without the typical risks associated with opioid use. Khak et al.[45] found that the majority of patients using MC for musculoskeletal pain had positive views of the therapy, with 93.7% agreeing or strongly agreeing that MC was effective in relieving their main symptoms. In an observational study conducted by Bakewell et al,[35] patients with lower back pain caused by lumbar spinal stenosis who took hemp-derived CBD gel caps with 0.3% THC experienced a clinically and statistically significant two-point decrease in the mean Pain Numeric Rating Scale (NPRS) over the study period. These improvements in pain also corresponded to improvements in quality-of-life measures and sleep. Glare et al[58] further confirmed MC's effectiveness in managing chronic back and neck pain, finding that medium (1.0 mL) and high (1.5 mL) dose oromucosal-administered MC, Cybis®, significantly reduced NRPS pain scores by 28.8% and 34.1%, respectively, over the study period.

In the management of osteoarthritis, MC has also indicated efficacy. In a randomized controlled trial evaluating CBD's effectiveness for managing thumb basal joint arthritis, Heineman et al[50] found that Visual Analog Score (VAS) pain and disability scores were significantly improved from baseline for the topical CBD group compared to the control group. Bawa et al.[51] also investigated the use of transdermal CBD for hand osteoarthritis. They found that patients' pain scores were significantly lower during the CBD gel application and washout phases compared with baseline. Patients' grip strength also increased during treatment compared with baseline. Another open-label study found that athletes who received topical CBD for their lower extremity injury experienced significant improvements in pain and their ability to return to normal life activities, highlighting a potential sports medicine application.[59]

The breadth of studies highlights MC's therapeutic potential but also underscores the heterogeneity of formulations and their specific use cases **[Table 1]**. While orthopedic patients most often turn to topical, oral, and inhaled MC,[45] there is no clear consensus as to which modalities are most appropriate for any musculoskeletal indication. In the absence of clear guidelines on how to offer MC to orthopedic patients, surgeons must exercise discretion, considering their patients' specific needs and how these align with the modalities' pharmacokinetic and clinical characteristics.

MC AND POSTOPERATIVE ORTHOPEDIC PAIN

In the context of immediate postoperative orthopedic pain relief, there is currently contradicting evidence and an overall paucity of literature. One randomized controlled

Table 1. Summary of Medical Cannabis Modalities, Pharmacokinetics, and Indications

Modality	Pharmacokinetics	Factors Affecting Bioavailability	Potential Orthopedic Indications	Other Indications
Inhalation	Onset: Rapid Peak Concentration: 3-15 Minutes Duration: 3-4 Hours	Gastric: No Hepatic: No	General musculoskeletal pain, osteoarthritis	General pain, neuropathic pain, HIV, nausea and vomiting, and multiple sclerosis spasticity
Oral	Onset: 0.5-1.5 Hours Peak Concentration: 2-4 Hours Duration: 5-12 Hours	Gastric: Yes Hepatic: Yes	General musculoskeletal pain, osteoarthritis, back and neck pain, postoperative pain	General pain, sleep, HIV, nausea and vomiting, and multiple sclerosis spasticity.
Oromucosal Spray	Onset: 5-30 Minutes Peak Concentration: 1-3 Hours Duration: 6-24 Hours	Gastric: No Hepatic: No	General musculoskeletal pain, back and neck pain	General pain, sleep, glaucoma, nausea and vomiting, and multiple sclerosis spasticity.
Topical	Onset: Variable Peak Concentration: 7-10 Days Duration: Upon Cessation	Gastric: No Hepatic: No	General musculoskeletal pain, basal thumb joint arthritis, osteoarthritis, sports medicine	Dermatological conditions

Data derived from previous references.[6,19,24-26,34,38,45,49-53,58-65]

trial by Haffar et al[66] found that postoperative topical application of CBD following total knee arthroplasty did not reduce pain or improve sleep scores. However, another randomized controlled trial by Alaia et al.[60] found that patients undergoing arthroscopic rotator cuff repair who received an oral, buccally absorbed CBD tablet three times per day experienced a significantly lower VAS pain score than the placebo group on postoperative day one. Patients in the CBD group also reported higher satisfaction with pain control compared to the control group on postoperative days one and two. In the one-year follow-up analysis from this research group, they confirmed that patients in the perioperative CBD group did not have any significant deficits in pain or self-reported satisfaction and outcomes compared to the placebo control group.[67] These findings validate the considerable heterogeneity in the existing literature, particularly with regard to the formulations, dosing regimens, and routes of administration of MC for postoperative orthopedic pain. Accordingly, future studies must prioritize procedure-specific trials to delineate the efficacy of different modalities and establish evidence-based dosing strategies that can be standardized in clinical practice.

MC'S ROLE IN COMBATING THE OPIOID CRISIS

MC is particularly relevant to the ongoing opioid crisis in the United States, defined by the misuse of prescription opioids, incidence of opioid use disorder, and increasing overdose deaths.[68] Orthopedic surgeons are among the highest prescribers of opioids[69] and they are at the front line of managing chronic nonsurgical and acute postoperative musculoskeletal pain, so reducing opioid use for orthopedic pain is crucial.

Opioid risks have led to a shift towards multimodal pain management strategies and increased use of non-opioid analgesics. Within this shifting landscape, MC has emerged as a promising adjunctive strategy that can mitigate opioid reliance. In a study by Greis et al,[61] patients with chronic lower back pain certified for MC had fewer filled opioid prescriptions and significantly reduced opioid consumption regardless of their baseline opioid usage. These opioid reductions were also accompanied by improvements in pain scores and daily function. Similarly, Renslo et al.[62] found that patients with osteoarthritic pain experienced a 43.6% average decrease in MME/day between six months pre-MC and six months post-MC use. This study also demonstrated clinically significant improvements in pain scores and Global Physical Health scores at 3 months post-MC initiation. Supporting these findings, a systematic review conducted by Okusanya et al.[63] revealed between a 64% to 75% reduction in opioid dosage for MC users with non-cancer chronic pain, and complete opioid cessation was achieved in up to 59.3% of patients. Therefore, MC as an adjunct in a multimodal pain management regimen could be key in mit-

igating the opioid crisis, particularly in orthopedic contexts with historically high opioid prescribing.

CHANGES IN PATIENT ATTITUDES TOWARDS MC

Despite the caution and stigma surrounding cannabis, recent surveys have shown that patients are increasingly receptive to MC to manage pain. Karakash et al.[64] found that 81.3% and 90.1% of orthopedic sports medicine patients were amenable to receiving THC or CBD-based products for their musculoskeletal pain, respectively. Additionally, 85.3% of the surveyed patients felt that cannabis-based products would be effective in combating the opioid crisis. In a cross-sectional survey conducted by Fones et al.,[65] approximately 10% of hand surgery patients used MC, and 80.9% of the remaining patients reported that they would consider its use to manage their chronic pain. The most common orthopedic conditions that patients considered using MC for included arthritis, back pain, tendon pain and inflammation, as well as postoperative pain. These findings highlight a growing willingness among orthopedic patients to consider MC as an alternative to traditional therapies to manage their musculoskeletal pain conditions.

MC'S EVOLVING LEGAL LANDSCAPE

MC's rapidly evolving legal landscape in the U.S. presents a challenge for orthopedic surgeons and other physicians. MC remains a Schedule I controlled substance under federal law. However, MC has been approved for medical use in 40 states, three territories, and the District of Columbia, creating a complex legal landscape in which state and federal laws conflict.[4] Further complicating this is the fact that MC's regulation differs across states and their various policies. As such, the feasibility and practicality of endorsing MC are significant concerns, particularly for practicing surgeons. Therefore, surgeons must remain educated on the current laws surrounding MC in their specific state, as well as be prudent regarding any new federal regulation changes. While surgeons may not be able to formally prescribe MC, they can play a critical role in discussing and expanding the current evidence base, outlining the potential benefits and risks, and helping patients navigate the various state-specific access pathways. Providing clear, informed communication can foster informed decision-making between patients and surgeons, ensuring that MC, when an option, can be implemented as part of a safe and effective multimodal approach to pain management.

CONCLUSION

MC has various modalities, pharmacokinetic considerations, and indications. However, its unique role within orthopedic surgery remains a crucial area of discussion. Evidence supports its potential in managing musculoskeletal and postoperative pain, and surveys suggest that orthopedic patients most often turn to topical, oral, and inhaled formulations. Still, the literature remains highly heterogeneous, therefore precluding consensus and making concrete conclusions difficult. This lack of standardization reveals the pressing need for clinical trials to help establish clear guidelines. MC may also reduce opioid consumption, which has significant public health implications related to the ongoing opioid crisis. As patient demand and legal acceptance expand, orthopedic surgeons must remain informed about local regulations and engage in patient-specific dialogue to advance the safe, evidence-based integration of MC into multimodal pain management plans.

DECLARATION OF CONFLICT OF INTEREST

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DECLARATION OF ETHICAL APPROVAL FOR STUDY

Given the review nature of the manuscript and the lack of patient information, there was no ethical approval process.

DECLARATION OF INFORMED CONSENT

There are no patient names, initials, hospital identification numbers, photographs, or any other form of protected health information in the submitted manuscript. Given the review nature of this manuscript, no formal informed consent process was conducted.

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REFERENCES

1. Crocq MA. History of cannabis and the endocannabinoid system. *Dialogues Clin Neurosci*. 2020;22(3):223-228. doi:10.31887/DCNS.2020.22.3/mcrocq

2. Dufton E. *Grass Roots: The Rise and Fall and Rise of Marijuana in America*. Basic Books; 2017.

3. Braun IM, Bohlke K, Abrams DI, et al. Cannabis and Cannabinoids in Adults With Cancer: ASCO Guideline. *J Clin Oncol*. 2024;42(13):1575-1593. doi:10.1200/JCO.23.02596

4. National Conference of State Legislatures. State Medical Cannabis Laws. www.ncsl.org. July 12, 2024. Accessed August 24, 2025. https://www.ncsl.org/health/state-medical-cannabis-laws

5. Kansagara D, Hill KP, Yost J, et al. Cannabis or Cannabinoids for the Management of Chronic Noncancer Pain: Best Practice Advice From the American College of Physicians. *Ann Intern Med*. 2025;178(5):714-724. doi:10.7326/ANNALS-24-03319

6. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA*. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

7. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515-521. doi:10.1212/01.wnl.0000253187.66183.9c

8. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672-680. doi:10.1038/npp.2008.120

9. Filippini G, Minozzi S, Borrelli F, Cinquini M, Dwan K. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. *Cochrane Database Syst Rev*. 2022;5(5):CD013444. doi:10.1002/14651858.CD013444.pub2

10. Monti MC, Frei P, Weber S, Scheurer E, Mercer-Chalmers-Bender K. Beyond Δ9-tetrahydrocannabinol and cannabidiol: chemical differentiation of cannabis varieties applying targeted and untargeted analysis. *Anal Bioanal Chem*. 2022;414(13):3847-3862. doi:10.1007/s00216-022-04026-2

11. Fournier G, Richez-Dumanois C, Duvezin J, Mathieu JP, Paris M. Identification of a new chemotype in Cannabis sativa: cannabigerol-dominant plants, biogenetic and agronomic prospects. *Planta Med*. 1987;53(3):277-280. doi:10.1055/s-2006-962705

12. Radwan MM, Chandra S, Gul S, ElSohly MA. Cannabinoids, Phenolics, Terpenes and Alkaloids of Cannabis. *Molecules*. 2021;26(9):2774. doi:10.3390/molecules26092774

13. Martinez Naya N, Kelly J, Corna G, Golino M, Abbate A, Toldo S. Molecular and Cellular Mechanisms of Action of Cannabidiol. *Molecules*. 2023;28(16):5980. doi:10.3390/molecules28165980

14. Bloomfield MA, Ashok AH, Volkow ND, Howes OD. The effects of Δ9-tetrahydrocannabinol on the dopamine system. *Nature*. 2016;539(7629):369-377. doi:10.1038/nature20153

15. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol*. 2007;150(5):613-623. doi:10.1038/sj.bjp.0707133

16. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *Br J Pharmacol*. 2015;172(20):4790-4805. doi:10.1111/bph.13250

17. O'Sullivan SE, Kendall DA. Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease. *Immunobiology*. 2010;215(8):611-616. doi:10.1016/j.imbio.2009.09.007

18. Maione S, Piscitelli F, Gatta L, et al. Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. *Br J Pharmacol*. 2011;162(3):584-596. doi:10.1111/j.1476-5381.2010.01063.x

19. Page RL 2nd, Allen LA, Kloner RA, et al. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. *Circulation*. 2020;142(10):e131-e152. doi:10.1161/CIR.0000000000000883

20. Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M. Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ9-Tetrahydrocannabinol. *Neuropsychopharmacology*. 2018;43(1):142-154. doi:10.1038/npp.2017.209

21. Solowij N, Broyd S, Greenwood LM, et al. A randomised controlled trial of vaporised Δ9-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects. *Eur Arch Psychiatry Clin Neurosci*. 2019;269(1):17-35. doi:10.1007/s00406-019-00978-2

22. Hudson R, Renard J, Norris C, Rushlow WJ, Laviolette SR. Cannabidiol Counteracts the Psychotropic Side-Effects of Δ-9-Tetrahydrocannabinol in the Ventral Hippocampus through Bidirectional Control of ERK1-2 Phosphorylation. *J Neurosci*. 2019;39(44):8762-8777. doi:10.1523/JNEUROSCI.0708-19.2019

23. 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(3):97-117. doi:10.1136/rapm-2022-104013

24. Gorelick DA. Cannabis-Related Disorders and Toxic Effects. *N Engl J Med*. 2023;389(24):2267-2275. doi:10.1056/NEJMra2212152

25. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol*. 2018;84(11):2477-2482. doi:10.1111/bcp.13710

26. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-360. doi:10.2165/00003088-200342040-00003

27. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther*. 2007;82(5):572-578. doi:10.1038/sj.clpt.6100200

28. Muheriwa-Matemba SR, Baral A, Abdshah A, et al. Cardiovascular and Respiratory Effects of Cannabis Use by Route of Administration: A Systematic Review. *Subst Use Misuse*. 2024;59(9):1331-1351. doi:10.1080/10826084.2024.2341317

29. Tashkin DP, Tan WC. Inhaled Marijuana and the Lung. *J Allergy Clin Immunol Pract*. 2022;10(11):2822-2829. doi:10.1016/j.jaip.2022.05.009

30. 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(12):1221-1232. doi:10.1016/j.jpain.2015.07.009

31. Almog S, Aharon-Peretz J, Vulfsons S, et al. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial. *Eur J Pain*. 2020;24(8):1505-1516. doi:10.1002/ejp.1605

32. Vinette B, Côté J, El-Akhras A, Mrad H, Chicoine G, Bilodeau K. Routes of administration, reasons for use, and approved indications of medical cannabis in oncology: a scoping review. *BMC Cancer*. 2022;22(1):319. doi:10.1186/s12885-022-09378-7

33. Azizoddin DR, Cohn AM, Ulahannan SV, et al. Cannabis use among adults undergoing cancer treatment. *Cancer*. 2023;129(21):3498-3508. doi:10.1002/cncr.34922

34. Zgair A, Wong JC, Lee JB, et al. Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. *Am J Transl Res*. 2016;8(8):3448-3459.

35. Bakewell BK, Sherman M, Binsfeld K, et al. The Use of Cannabidiol in Patients With Low Back Pain Caused by Lumbar Spinal Stenosis: An Observational Study. *Cureus*. 2022;14(9):e29196. doi:10.7759/cureus.29196

36. Keating GM. Delta-9-Tetrahydrocannabinol/Cannabidiol Oromucosal Spray (Sativex®): A Review in Multiple Sclerosis-Related Spasticity. *Drugs*. 2017;77(5):563-574. doi:10.1007/s40265-017-0720-6

37. Hua S. Advances in Nanoparticulate Drug Delivery Approaches for Sublingual and Buccal Administration. *Front Pharmacol*. 2019;10:1328. doi:10.3389/fphar.2019.01328

38. Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. *Eur J Clin Pharmacol*. 2013;69(5):1135-1147. doi:10.1007/s00228-012-1441-0

39. Itin C, Barasch D, Domb AJ, Hoffman A. Prolonged oral transmucosal delivery of highly lipophilic drug cannabidiol. *Int J Pharm*. 2020;581:119276. doi:10.1016/j.ijpharm.2020.119276

40. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. *Clin Pharmacokinet*. 2002;41(9):661-680. doi:10.2165/00003088-200241090-00003

41. Überall MA. A Review of Scientific Evidence for THC:CBD Oromucosal Spray (Nabiximols) in the Management of Chronic Pain. *J Pain Res*. 2020;13:399-410. doi:10.2147/JPR.S240011

42. Motaghi E, Ghasemi-Pirbaluti M, Rashidi M, Alasvand M, Di Ciano P, Bozorgi H. The effect of tetrahydrocannabinol:cannabidiol oromucosal spray on cognition: a systematic review. *Eur J Clin Pharmacol*. 2023;79(3):371-381. doi:10.1007/s00228-023-03454-y

43. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*. 2017;318(17):1708-1709. doi:10.1001/jama.2017.11909

44. Cash MC, Cunnane K, Fan C, Romero-Sandoval EA. Mapping cannabis potency in medical and recreational programs in the United States. *PLoS One*. 2020;15(3):e0230167. doi:10.1371/journal.pone.0230167

45. Khak M, Ramtin S, Chung J, Ilyas AM, Greis A. Patterns, Efficacy, and Cognitive Effects of Medical Cannabis Use in Chronic Musculoskeletal Pain Patients. *Cureus*. 2025;17(5):e84102. doi:10.7759/cureus.84102

46. Tijani AO, Thakur D, Mishra D, Frempong D, Chukwunyere UI, Puri A. Delivering therapeutic cannabinoids via skin: Current state and future perspectives. *J Control Release*. 2021;334:427-451. doi:10.1016/j.jconrel.2021.05.005

47. Mahmoudinoodezh H, Telukutla SR, Bhangu SK, Bachari A, Cavalieri F, Mantri N. The Transdermal Delivery of Therapeutic Cannabinoids. *Pharmaceutics*. 2022;14(2):438. doi:10.3390/pharmaceutics14020438

48. Hess C, Krämer M, Madea B. Topical application of THC containing products is not able to cause positive cannabinoid finding in blood or urine. *Forensic Sci Int*. 2017;272:68-71. doi:10.1016/j.forsciint.2017.01.008

49. Zamarripa CA, Tilton HE, Lin S, et al. Pharmacokinetics and pharmacodynamics of five distinct commercially available hemp-derived topical cannabidiol products. *J Anal Toxicol*. 2024;48(2):81-98. doi:10.1093/jat/bkae001

50. Heineman JT, Forster GL, Stephens KL, Cottler PS, Timko MP, DeGeorge BR Jr. A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis. *J Hand Surg Am*. 2022;47(7):611-620. doi:10.1016/j.jhsa.2022.03.002

51. Bawa Z, Lewis D, Gavin PD, et al. An open-label feasibility trial of transdermal cannabidiol for hand osteoarthritis. *Sci Rep*. 2024;14(1):11792. doi:10.1038/s41598-024-62428-x

52. Frane N, Stapleton E, Iturriaga C, Ganz M, Rasquinha V, Duarte R. Cannabidiol as a treatment for arthritis and joint pain: an exploratory cross-sectional study. *J Cannabis Res*. 2022;4(1):47. doi:10.1186/s42238-022-00154-9

53. Ramer R, Hinz B. Cannabinoid Compounds as a Pharmacotherapeutic Option for the Treatment of Non-Cancer Skin Diseases. *Cells*. 2022;11(24):4102. doi:10.3390/cells11244102

54. Kwiecień E, Kowalczuk D. Therapeutic Potential of Minor Cannabinoids in Dermatological Diseases-A Synthetic Review. *Molecules*. 2023;28(16):6149. doi:10.3390/molecules28166149

55. Martins AM, Gomes AL, Vilas Boas I, Marto J, Ribeiro HM. Cannabis-Based Products for the Treatment of Skin Inflammatory Diseases: A Timely Review. *Pharmaceuticals (Basel)*. 2022;15(2):210. doi:10.3390/ph15020210

56. Ahmed B, Kaur S, Naryal S, et al. Nanoformulated cannabidiol for skin disorders: A GRADE-based systematic review of therapeutic evidence and efficacy. *Eur J Pharm Biopharm*. Published online June 13, 2025. doi:10.1016/j.ejpb.2025.114784

57. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2 Suppl):S105-S120. doi:10.36076/ppj.2008/11/S105

58. Glare P, Chye R, Bloch M, Arya M, Moore A, Montgomery J. Tolerability and Efficacy of a 10:25 Preparation of Δ9-Tetrahydrocannabinol and Cannabidiol for Treatment of Chronic Back or Neck Pain: A Multiple-Dose Escalation Study. *Med Cannabis Cannabinoids*. 2023;6(1):66-76. doi:10.1159/000531232

59. Hall N, James B, Bhuiyan MAN, Crane E, Falgout C, Murnane KS. Topical cannabidiol is well tolerated in individuals with a history of elite physical performance and chronic lower extremity pain. *J Cannabis Res*. 2023;5(1):11. doi:10.1186/s42238-023-00179-8

60. Alaia MJ, Hurley ET, Vasavada K, et al. Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved Satisfaction Immediately After Arthroscopic Rotator Cuff Repair: A Placebo-Controlled, Double-Blinded, Randomized Trial. *Am J Sports Med*. 2022;50(11):3056-3063. doi:10.1177/03635465221109573

61. Greis A, Renslo B, Wilson-Poe AR, Liu C, Radakrishnan A, Ilyas AM. Medical Cannabis Use Reduces Opioid Prescriptions in Patients With Chronic Back Pain. *Cureus*. 2022;14(1):e21452. doi:10.7759/cureus.21452

62. Renslo B, Greis A, Liu CS, Radakrishnan A, Ilyas AM. Medical Cannabis Use Reduces Opioid Prescriptions in Patients With Osteoarthritis. *Cureus*. 2022;14(1):e21564. doi:10.7759/cureus.21564

63. Okusanya BO, Asaolu IO, Ehiri JE, Kimaru LJ, Okechukwu A, Rosales C. Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review. *Syst Rev*. 2020;9(1):167. doi:10.1186/s13643-020-01425-3

64. Karakash WJ, Bolia IK, Levian BA, et al. Orthopedic Patients Are Highly Amenable to Cannabis-Based Products for the Treatment of Musculoskeletal Pain. *Orthopedics*. 2025;48(2):98-103. doi:10.3928/01477447-20250114-02

65. Fones L, Townsend C, Hoyen H, et al. Hand Surgery Patient Perspectives on Medical Cannabis: A Survey of Over 600 Patients. *J Hand Surg Glob Online*. 2022;5(1):102-107. doi:10.1016/j.jhsg.2022.02.009

66. Haffar A, Khan IA, Abdelaal MS, Banerjee S, Sharkey PF, Lonner JH. Topical Cannabidiol (CBD) After Total Knee Arthroplasty Does Not Decrease Pain or Opioid use: A Prospective Randomized Double-Blinded Placebo-Controlled Trial. *J Arthroplasty*. 2022;37(9):1763-1770. doi:10.1016/j.arth.2022.03.081

67. Alaia MJ, Li ZI, Chalem I, et al. Cannabidiol for Postoperative Pain Control After Arthroscopic Rotator Cuff Repair Demonstrates No Deficits in Patient-Reported Outcomes Versus Placebo: 1-Year Follow-up of a Randomized Controlled Trial. *Orthop J Sports Med*. 2024;12(2):23259671231222265. doi:10.1177/23259671231222265

68. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*. 2017;167(5):293-301. doi:10.7326/M17-0865

69. Guy GP Jr, Zhang K. Opioid Prescribing by Specialty and Volume in the U.S. *Am J Prev Med*. 2018;55(5):e153-e155. doi:10.1016/j.amepre.2018.06.008