ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

Cannabis Science and Therapeutics: An Overview for Clinicians

The Journal of Clinical Pharmacology
2024, 0(0) 1–15

DOI: 10.1002/jcph.2400

Leah Sera, PharmD, MA, BCPS and Carrie Hempel-Sanderoff, DO

Abstract

Cannabis-based therapeutics have garnered increasing attention in recent years as patients seek alternative treatments for various medical conditions. This narrative review provides a comprehensive overview of the science behind the medical use of cannabis, focusing on the medical evidence for commonly treated conditions. In addition, the review addresses the practical considerations of using cannabis as a therapeutic agent, offering insights into dosing strategies, variations in cannabinoid formulation, and individual patient responses. Precautions, adverse consequences, and drug interactions are also discussed, with a focus on patient safety and the potential risks associated with cannabis use.

Although cannabis (*Cannabis sativa*) has had a place in many cultures since ancient times, its role as a therapeutic agent in modern times has a convoluted history. Writings from Egypt, China, and India indicate its use as a medicinal agent, perhaps as early as 2350 B.C.[1] After a brief period in which Western cultures used cannabis in the treatment of several conditions, cannabis was essentially prohibited in the United States in 1938 and made illegal by the Controlled Substances Act of 1970.[2] In 1996, California legalized cannabis for medical use,[3] and since that time, there has been a growing wave of interest, driven mainly by changing public opinion, in exploring the pharmaceutical and clinical science of the cannabis plant. This narrative review will introduce the pharmacology of the cannabis plant, summarize the medical evidence evaluating several conditions for which patients commonly seek treatment with cannabis, and provide practical information for clinicians working with patients who use cannabis.

The Endocannabinoid System

The endocannabinoid system (ECS) is an extensive network of receptors, their endogenous ligands, and enzymes that synthesize and degrade those ligands.[4] The ECS appears to be involved in modulating many biological functions in mammalian species, including sleep, memory, mood, learning, hunger and feeding, and pain.[5,6] The widespread distribution of 2 G-protein-coupled receptors (GPCRs) – cannabinoid (CB) 1 and CB2 – throughout the human body suggests that the role of the ECS has yet to be fully understood. CB1 receptors are concentrated in the central nervous system, but CB1 receptors have also been identified in the periphery, including in cardiac tissue, reproductive organs, and the gastrointestinal tract.[7] CB2 receptors are concentrated in peripheral tissues, particularly in the immune system.[8]

The cannabinoid receptors are modulated by fatty acid neurotransmitters termed *endocannabinoids* or *endogenous cannabinoids*. The most well-studied endocannabinoids are anandamide and 2-arachidonylglycerol.[9] These lipophilic molecules are synthesized on demand in the postsynapse and bind to presynaptic CB receptors, modulating the release of neurotransmitters. The synthesis of endocannabinoids results from the activation of other GPCRs in the central nervous system, including glutamate and serotonin receptors.[10] In addition to the CB receptors, endocannabinoids appear to interact with myriad other receptors, including transient receptor potential (TRP) ion channels, peroxisome proliferator-activated nuclear receptors, and orphan GPCRs.[7,11] An expanded view of the ECS that includes the endocannabinoids and related molecules, their biosynthetic and metabolic pathways, and the many receptors with which they interact is termed the *endocannabinoidome*.[12]

Department of Practice, Sciences, and Health Outcomes Research, University of Maryland School of Pharmacy, Baltimore, MD, USA

Submitted for publication 18 October 2023; accepted 15 December 2023.

Corresponding Author:
Leah Sera, PharmD, MA, BCPS, Department of Practice, Sciences, and Health Outcomes Research, University of Maryland School of Pharmacy, 20 N. Pine St, Baltimore, MD 21201.
E-mail: lsera@rx.umaryland.edu

The Cannabis Plant and Its Components

The cannabis plant comes from the same botanical family (Cannabaceae) as the hops plant, which is used in brewing beer.[13] Traditionally, cannabis species were classified according to morphological characteristics (ie, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*).[1] There are anecdotal claims that sativa and indica have differing psychoactive effects. However, the pharmacology of the plant cannot be ascertained by studying its morphology alone. In the words of Ethan Russo, a physician and renowned cannabis researcher, "the sativa/indica distinction as commonly applied in the lay literature is total nonsense and an exercise in futility."[14] Additionally, so much crossbreeding, both inadvertent and purposeful, has occurred that most cannabis plants grown today are hybrids and difficult to classify as any specific botanical species.[15]

Cannabinoids

The cannabis plant contains hundreds of chemicals, including CBs, terpenes, flavonoids, and others, many of which may affect human physiology. CBs are lipophilic molecules that interact with the CB receptors and are produced primarily by the cannabis plant, while terpenes and flavonoids are nonspecific chemicals that are responsible for the odor, color, and flavor of many plant species.[16,17] CBs may be found in the glandular trichomes (hairlike structures) on the flowers of female cannabis plants.[13,18] The most well-studied CBs are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Other predominant, if less well-studied, cannabinoids include cannabigerol, cannabinol, and cannabichromene.[19] CBs primarily exist in the plant as acids (eg, tetrahydrocannabinolic acid, cannabidiolic acid) and are decarboxylated to their neutral (ie, nonacid) forms when exposed to heat.[19]

THC is a partial agonist at CB1 and CB2 receptors and, like the endocannabinoids, may interact with noncannabinoid receptors. THC is most well known for its psychoactive effects, which appear to be mediated primarily by the CB1 receptor and downstream modulation of gamma-aminobutyric acid, glutamine, and dopamine.[20] In this article, the term *psychoactive* refers to the pharmacologic alteration of mood, perception, emotion, or cognition. However, THC also has therapeutic applications, including as an analgesic and antiemetic, that have been well studied in clinical trials.[13] Additionally, the upregulation of CB receptors in cells and tissues associated with cancer, stroke, epilepsy, and gastrointestinal inflammation[21] suggests a role for THC in the modulation of these disease states, although robust supporting clinical data are lacking. THC is also responsible for several adverse effects of cannabis consumption, including anxiety, sedation, and increased risk for cannabis use disorder.[19,22] The increasing concentration of THC in cannabis plants and products over the past several decades[23] may be increasing rates of more serious adverse reactions such as acute psychosis and cannabis hyperemesis syndrome.[22,24]

CBD does not have psychoactive effects and, unlike THC, has a very low affinity for CB receptors.[13] The pharmacological effects of CBD may be mediated through multiple mechanisms, including inhibiting the degradation of endocannabinoids, interaction with serotonin receptors, and modulation of adenosine signaling pathways.[13] CBD is effective as an antiepileptic, and limited clinical evidence supports its use in other conditions such as Parkinson disease, autism, and smoking cessation.[25] Anecdotal evidence suggests that CBD may attenuate the psychoactive effects of THC, but clinical evidence does not support this claim.[26]

Terpenes and Flavonoids

Much attention has been given in recent years to the terpene component of cannabis plants and products. Terpenes are phytochemicals that give a plant a distinct aroma, and it has been postulated that these molecules may also have the potential to beneficially affect human physiology. Terpenes commonly identified in cannabis plants include beta-myrcene, alpha-pinene, limonene, and beta-caryophyllene. Like CBs, terpenes are lipophilic and cross the blood-brain barrier.[19] The majority of scientific research into the therapeutic potential of terpenes has been preclinical in nature, with various terpenes showing anticancer, antimicrobial, anti-inflammatory, antioxidant, analgesic, neuroprotective, and anxiolytic activity.[27,28] Clinical studies of terpenes unrelated to cannabis have yielded interesting results. Inhalation of limonene, the terpene associated with a citrus aroma, may be associated with attenuating depression in hospitalized patients.[27] Inhalation of caryophyllene, the terpene associated with a peppery or spicy aroma, significantly reduced the craving for cigarettes.[29]

The Entourage Effect

The *entourage effect* is a term coined by iconic cannabis researcher Raphael Mechoulam and his team in the 1990s to describe the purported synergistic effect of whole-plant or full-spectrum formulations of cannabis versus single cannabinoid compounds.[30] These researchers noted that the activity of 2-arachidonylglycerol at CB receptors was significantly enhanced by esters that, on their own, had no pharmacological activity at the receptor.[30] Since this discovery, many preclinical studies and a few clinical trials have attempted to elucidate the mechanisms and importance of this effect. Two preclinical studies determined that the most common terpenes in cannabis do not affect

Table 1. Selected Characteristics of Cannabis Dosage Forms[93,121]

Formulation	Onset	Duration	Pro/con
Inhaled (smoked or vaporized flower)	5-10 minutes	2-4 hours	Pro: rapid onset, may be helpful for acute symptoms Con: combustion and smoking irritants, inconsistent dosing
Oral	1-3 hours	6-8 hours	Pro: convenient, discrete, simple dosing Con: highly variable absorption, effects may be hard to predict
Oromucosal	15-45 minutes	6-8 hours	Pro: more rapid onset than oral form, pharmaceutical form with documented efficacy exists Con: not widely available, expensive
Transdermal	1-7 hours	Up to 24-72 hours	Pro: alternative to smoking or oral formulations, less frequent dosing required Con: unpredictable absorption and duration of action, not widely available, expensive

the activity of phytocannabinoids at CB receptors or TRP channels.[31,32] The few published clinical trials comparing whole-plant to isolated cannabinoid formulations vary in methodology and outcomes.[33] Additionally, data from observational studies and randomized controlled trials (RCTs) often conflict, and the products, concentrations, and administration methods used in RCTs often are not representative of real-world conditions, calling the generalizability of such data into question.[33] Questions for future research into the existence of the entourage effect include the effects of CBD on THC metabolism, the effects of terpenes on CB absorption, and further clinical trials comparing the effects of whole-plant, full-spectrum, or broad-spectrum formulations to CB isolates.[30]

The Therapeutic Uses of Cannabis-Based Medicines

Cannabis-based medicines are available in a wide variety of formulations (Table 1). Cannabis and CB products available for medical use include whole-plant products (ie, dried flower), artisanal products (tinctures, extracts, oromucosal formulations, topical and transdermal formulations, and infused foods or "edibles"), and synthetic or plant-derived pharmaceutical products. A review of the regulatory landscape pertaining to cannabis products is beyond the scope of this review, but in summary, pharmaceutical products may be obtained with a valid prescription at pharmacies in the United States, while whole-plant and artisanal formulations are available from stores only in states that have legalized cannabis for medical or recreational use since cannabis is largely still illegal at the federal level at the time of this writing. Individuals who desire to be registered as a medical cannabis patient must be certified by a registered health care provider to have a condition that qualifies them for medical cannabis use (ie, a "qualifying condition").[34] Providers in the United States cannot legally prescribe cannabis due to its Schedule I status (a classification indicating that a drug has "no currently accepted medical use and a high potential for abuse")[35]; however, they can recommend its use in states where it is legal.[34] The state regulatory body responsible for implementing cannabis policies in each state determines which conditions and disease states are considered qualifying conditions.

The 2017 National Academies of Sciences, Engineering, and Medicine (NASEM) report on the Health Effects of Cannabis and Cannabinoids classified disease states as having conclusive, substantial, limited, or no/insufficient evidence supporting cannabis use (Table 2).[13] In states where medical cannabis is legal, chronic pain is by far the most often reported reason for use; in 2020, it was the most common qualifying condition for medical cannabis patients in 26 states and the District of Columbia.[36] Between 2016 and 2020, the percentage of patients with qualifying conditions classified as having limited or insufficient evidence for use increased from 15.4% to 31.4%. Such conditions include posttraumatic stress disorder, as well as vague descriptions such as "other" and "psychiatric condition."[36] A national, online, anonymous survey of 9003 adults in the United States found that of the 591 respondents who reported using cannabis for medical purposes, the most common reasons for use were anxiety (49%), insomnia (47%), chronic pain (42%), and depression (39%).[37] The evidence base for these 4 indications is discussed below. Of note, use of hemp-derived CBD products among US adults has skyrocketed since production of hemp was legalized in the 2018 Farm Bill, with sales increasing from $108 million in 2014 to $1.9 billion in 2022.[38] The most common reasons for consuming CBD include anxiety, insomnia, and pain,[38] despite little or no evidence supporting the use of CBD for these indications.

Chronic Noncancer Pain

The ECS is intricately involved in pain perception and pain modulation, with endocannabinoids and CB receptors found in peripheral tissues, the spinal cord, and areas of the brain associated with nociception.[39]

Table 2. The Evidence Base for Cannabinoid Therapy[13,41,138,139]

Level of evidence	Symptom/condition	Formulation(s) associated with therapeutic benefit			
		THC	CBD	THC:CBD (1:1)	Inhaled flower
Conclusive or substantial evidence of effectiveness • Strong evidence from RCTs (conclusive) • Strong evidence from many (conclusive) or several (substantial) good-quality studies • Very few or no credible opposing findings	Chronic pain			x	x
	Chemotherapy-induced nausea and vomiting	x			
	Multiple sclerosis–associated spasticity (patient-reported symptoms)	x		x	
	Seizures associated with Lennox-Gastaut and Dravet syndromes		x		
Moderate evidence of effectiveness • Several findings from good- to fair-quality studies • Very few or no credible opposing findings • Some uncertainty due to chance or bias	Insomnia	x			
Limited evidence of effectiveness • Supportive findings from fair-quality studies • Mixed findings, with most favoring effectiveness • Substantial uncertainty due to chance or bias	HIV/AIDS-associated anorexia/cachexia	x			x
	Multiple sclerosis–associated spasticity (clinician-measured symptoms)	x		x	
	Symptoms associated with: • Tourette syndrome • Social anxiety disorder • Posttraumatic stress disorder	x x	x		
No evidence or insufficient evidence • Mixed findings or a single poor-quality study or health outcomes have not been studied • No conclusion can be made due to chance or bias	Cancer Cancer-associated anorexia/cachexia Anorexia nervosa Spasticity associated with spinal cord injury Substance use disorders Dystonia Schizophrenia Symptoms associated with: • Huntington disease • Amyotrophic lateral sclerosis • Parkinson disease				

CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol.

Endocannabinoids and phytocannabinoids have demonstrated antinociceptive effects in animal models of acute pain, inflammatory pain, and neuropathic pain.[40]

The NASEM systematic review published in 2017 classified chronic pain as being an indication for which there was substantial evidence supporting the use of cannabis or synthetic THC.[13] A more recent systematic review, published in 2022, stratified placebo-controlled RCTs according to their THC:CBD ratios (high, comparable, or low), as determined by a panel of experts, as well as classifying products as plant-derived or synthetic.[41] The meta-analysis of studies included in this systematic review found that synthetic products with high THC:CBD ratios (eg, dronabinol, nabilone) were associated with a moderately beneficial effect on pain severity as measured on a scale of 0-10 as well as an increased risk for sedation. The authors were unable to draw conclusions about the effects of high THC:CBD plant-derived products due to the high degree of heterogeneity in those study designs. Comparable THC:CBD products produced small beneficial effects on pain severity, with an increased risk for dizziness, sedation, and nausea. Insufficient evidence was available to draw conclusions about low THC:CBD products, including oral and topical formulations.

Given increasing concerns over the past several years about the use of opioids for the treatment of chronic pain and the risk for opioid abuse and diversion,[42] there has been considerable interest in whether medical cannabis could replace or reduce opioids for such patients. A recent systematic review found that low-level evidence from observational studies suggests that cannabis-based medicines are associated with a reduction in opioid use.[43] However, RCTs evaluating the effect of cannabis-based medicine on chronic pain did not support this association because the methodology of these studies included requiring patients to maintain their current opioid dose.[43]

Anxiety

The role of the ECS in modulating mood is well-documented in animal studies.[44] Anxiolytic effects are mediated by the CB1 receptor. The effect of CB1

activation appears to be biphasic, with low doses of exogenous CBs providing positive benefits and higher doses being anxiogenic.[45] Despite being a common reason for patients to seek treatment with medical cannabis, very little clinical evidence exists to support or refute its therapeutic role. The NASEM report concluded that there is limited evidence supporting the use of CBD for the treatment of social anxiety disorders.[13]

A systematic review identified 5 small, prospective RCTs evaluating the use of cannabis-based medicine in people with generalized anxiety disorder or social anxiety disorder.[46] Of these, CBD was evaluated as a treatment for social anxiety disorder in 3 studies (N = 71), and the synthetic THC analog nabilone was evaluated in the treatment of generalized anxiety disorder (N = 28). Once-weekly nabilone (0.5-5 mg) over a 5-week period did not result in improvements in anxiety symptoms, while daily nabilone (3 mg) over a 1-month period significantly improved mild anxiety symptoms compared to placebo.[47] Single-dose CBD (600 mg) was effective in reducing social anxiety symptoms when given prior to a simulated public speaking test,[48] and CBD 300 mg daily given for 4 weeks significantly improved social anxiety symptoms compared to placebo.[49] Adverse effects from nabilone included dry mouth, sedation, increased heart rate, and orthostatic hypotension; adverse effects were not evaluated in any of the CBD studies.[46] Some studies evaluating the use of cannabis-based medicine or synthetic cannabinoids for chronic pain also assessed the effect on anxiety as a secondary outcome.[50] These studies suggested that dronabinol, nabilone, and nabiximols improved anxiety symptoms in patients with chronic pain to a greater extent than placebo.[50]

Insomnia

Although it is well known that cannabis use is associated with somnolence,[51] the role of CBs and the ECS in the regulation of sleep has yet to be fully elucidated. Preclinical studies suggest that the diurnal nature of endocannabinoid levels may influence the sleep-wake cycle.[51] In animal models, manipulating the ECS by administering endocannabinoids or by modulating enzyme levels may promote or inhibit sleep.[51] A systematic review of studies evaluating the effect of cannabis on sleep found that 38% of RCTs and 58% of nonrandomized trials had positive results (ie, improved sleep quality or quantity, shorter sleep onset, higher percentage of time in rapid eye movement sleep).[52] The studies included in this review evaluated CBD, THC, dronabinol, nabilone, and formulations that combined CBD and THC; no significant difference in effectiveness was found between CBD and THC formulations.[52] Heterogeneity of included studies precluded performing a meta-analysis.[52] Chronic use of cannabis may lead to tolerance to sleep-promoting effects, necessitating dose titration to maintain effectiveness, and abrupt cessation of cannabis in chronic users may lead to sleep disruption.[51,53]

Depression

Although depression is one of the most common symptoms for which people obtain medical cannabis, there is very little data, either preclinical or clinical, giving insight into the therapeutic uses or mechanisms of purported effects. Though preclinical studies do suggest relationships between mood, CB receptor density, and endocannabinoid levels, it is hard to draw conclusions about these associations, since such studies indicate that modulation of the ECS may have either pro- or antidepressant effects.[54] In humans, phytocannabinoids may be used to manage depressive symptoms; however, individuals with cannabis use disorder are at greater risk for developing mood disorders such as unipolar and bipolar depression.[55] Some of the most compelling data came from clinical trials of the failed antiobesity drug rimonabant.[44] Rimonabant is a CB1 receptor antagonist developed as an anorectic agent. Although the drug performed well as a weight-loss therapy, it significantly increased the risk of adverse psychiatric effects such as depression and anxiety, including 2 deaths from suicide, and was never approved by the US Food and Drug Administration (FDA).[56] In clinical trials, cannabis did not have any effect on depressive symptoms in patients with chronic pain or spasticity, and no RCTs published have evaluated cannabis for depression as a primary outcome.[13,57]

The Clinician's Approach to the Patient Using Cannabis

The clinician's role in caring for patients using medical cannabis to manage a chronic health condition remains perplexing due to the evolving landscape of federal cannabis policies, the wide variety of individual state programs governing cannabis access, and the paucity of professional education and training.[58] This phenomenon is contrary to the current evidence of clinician perceptions of cannabis' efficacy and support for its use. A recent survey of primary care physicians by Abo Ziad et al in 2022 illustrates the paradoxical attitudes and practices of US clinicians. In the survey, more than 78% of physicians supported the use of medical cannabis and about 63% supported its legalization.[59] About 84% of the physicians believed that medical cannabis helped patients with cancer, and 82% believed it helped chronic pain. However, in the same group, only 28.3% believed that family physicians should recommend the use of medical cannabis.[59] The resulting knowledge gaps and conflicting practice

approaches present ongoing challenges for clinicians caring for patients using medical cannabis.

As the legal framework around cannabis access continues to shift, modern clinicians must independently cultivate competence and scientific understanding of the ECS and its modulators as they relate to the clinical use of CBs, topics not traditionally taught in health professions education programs. Rapidly increasing numbers of patients are using medical cannabis products to manage their pain and symptoms from chronic illness. At the time of this writing, medical cannabis is legal in some form in 47 states, 3 US territories, and the District of Columbia.[60] An estimated 3 million Americans use cannabis for relief of a variety of illnesses, and this figure is expected to grow with further policy changes.[60] The 2021 National Survey on Drug Use and Health revealed that 18.7% of people aged 12 years or older (about 52.5 million people) reported using cannabis in the past 12 months.[61]

A proposed clinician approach to caring for patients using medical cannabis should address widespread knowledge gaps around medical cannabis science, along with cultivating cautious and informed interpretation of clinical evidence.[58,59] Clinicians should also be mindful of local and federal policy changes affecting their patient population and state. In addition, clinicians must feel empowered to provide quality education about cannabis science while minimizing stigma, fears of liability, and perceived professional risk.

The Clinician-Patient Relationship

The protective mechanism of the clinician-patient relationship provides a framework for clinicians to counsel patients on the expected effects of medical cannabis. Dispelling myths and clarifying appropriate language and terminology around clinician practices are vital in moving forward. As described above, doctors can recommend medical cannabis in states where cannabis is legal after determining and certifying that the patient suffers from one of the conditions the state's law deems to warrant medical cannabis.[35] The US Court of Appeals upheld the protection of this recommendation practice for the Ninth Circuit in *Conant v. Walters*, which ruled that a physician's discussing the potential benefits of medicinal marijuana and making such recommendations constitute protected speech under the First Amendment reinforcing that unrestricted communication is vital in preserving the clinician-patient relationship and ensuring proper treatment.[62]

Based on this precedent, clinicians should move forward more confidently with activities such as counseling, educating their patients on the ECS, and explaining the scientific evidence available to guide medical cannabis use. Increased professional risk comes with clinicians who pursue financial involvement and relationships in the cannabis industry, such as owning a dispensary or facilitating the sale of cannabis, which may be considered "aiding and abetting."[62]

Harm Reduction

A primary concern for clinicians is the potential for harm related to cannabis use. Recent research has more clearly defined some specific areas of risk and vulnerability around cannabis use.

Risk of Addiction

Cannabis use disorder (CUD) is a concerning occurrence among cannabis users. While the true prevalence varies, recent surveys indicate that in 2021, an estimated 5.8% (or about 16.3 million people) reported a CUD in the past 12 months. Other estimates indicate rates of CUD approaching 10%.[63] CUD is characterized similarly to other substance use disorders. It is often associated with dependence – in which a person feels withdrawal symptoms when not taking the substance, along with continued cannabis use despite negative consequences.[63] People who use cannabis daily or frequently report a withdrawal syndrome including irritability, mood, sleep difficulties, decreased appetite, cravings, restlessness, or various symptoms of physical discomfort that peak within the first week after quitting and last up to 2 weeks.[64]

Cannabis potency (ie, THC concentration) appears to be a clear factor in the development of CUD. A recent systematic review of observational studies examined the association between cannabis potency and addiction. Use of high-potency cannabis was associated with a 7-times increased risk of dependence syndrome in a sample of Japanese patients and a 4-times increased risk of problematic use in a sample of patients in the United Kingdom compared with those who used lower-potency cannabis.[65] A 2022 systematic review showed that the risk of CUD increases as the frequency of cannabis use increases. The risk of CUD was 4 times more likely in monthly cannabis users, 8 times more likely in weekly users, and 17 times more likely in daily users.[66] While further high-quality data are needed, it appears that specific cannabis use patterns may increase the risk of CUD, namely, increased frequency of cannabis consumption and high-potency THC use, which should encourage clinicians to monitor for these parameters and counsel patients to avoid high-potency cannabis.[63]

Risk of Psychosis

The occurrence of psychosis and psychotic disorders is another concerning effect of cannabis use. The psychoactive properties of cannabis and THC create a dose-dependent degree of impairment and intoxication that can precipitate temporary or chronic psychosis

in vulnerable users.[67] A recent study of a large international sample of cannabis users (N = 233,475) found that 0.47% of cannabis users reported lifetime occurrence of cannabis-associated psychotic symptoms, requiring emergency medical treatment following the use of cannabis.[68] Risk was elevated in those using predominantly high-potency resin, those mixing cannabis with tobacco, and those with a preexisting diagnosis of psychosis, bipolar disorder, anxiety, or depression.[68] Patients with first-episode psychosis are more likely to use higher-potency cannabis,[69] with younger age of first cannabis use.[70] Genetic influences appear to increase the risk of psychosis in vulnerable groups. Carvalho et al. demonstrated associations with genetic polymorphisms and modulations of genes involved directly or indirectly with dopamine pathways.[67] While this warrants further investigation with ongoing studies, genetic influences, young age, family history of psychosis, schizophrenia, or other mental health diagnosis, and frequent use of high-potency THC appear to be risk factors for the development of cannabis-associated psychosis.

Risk During Pregnancy

Cannabis use during pregnancy remains a polarizing topic. The self-reported prevalence of cannabis use during pregnancy ranges from 2% to 5%. Notably, 34%-60% of cannabis users continue to use during pregnancy, with many women believing that it is relatively safe to use during pregnancy and less expensive than tobacco.[71] Cannabis use has a negative effect on fetal development and pregnancy outcomes. In recent large systematic reviews, prenatal cannabis use was associated with greater odds of preterm birth, small-for-gestational-age, and perinatal mortality even after accounting for prenatal tobacco use.[71,72] THC crosses the placenta and can result in fetal blood levels of THC comparable to maternal blood levels.[73] The fetal ECS plays a key role in regulating and signaling the embryonic development of neural cells in functional areas such as the forebrain and hippocampus.[74] THC exposure appears to influence axon morphology and development, which may increase the incidence of limitations in higher cognitive functioning and an increased risk of neuropsychiatric disorders.[75] Infants born by mothers using cannabis appear to have increased body movements, stronger startle reflexes, and decreased quality sleep cycles.[43,76] Research on the later impacts of cannabis on child and adolescent cognition, IQ, and psychological health remains conflicting[77,78] and warrants further long-term studies. Cannabis use remains medically contraindicated during pregnancy, and pregnant women should be counseled on the risks and discouraged from using cannabis.[79]

Clinically Significant Drug-Drug Interactions

Clinicians must be increasingly aware of the potential for drug-drug interactions between cannabis products and common pharmaceuticals. Many patients with chronic illness are taking multiple prescription medications, and there have been limited data to inform recommendations or monitoring. THC and CBD are metabolized in the liver by the cytochrome P450 (CYP) family of enzymes.[80] The effects of THC and CBD can be additive, synergistic, or antagonistic in the presence of other medications.[80] Generally, the interactions reported in the literature are explained by a pharmacokinetic mechanism due to changes in the activity of the CYP enzyme glycoprotein P or other drug transporters.[81] Currently, most reported cannabis-drug interactions lack clinical trial results, and are challenging to generalize due to variable routes of administration and recreational use.[80]

A significant clinical interaction is seen between warfarin and cannabis. Case reports described gastrointestinal bleeding and increased international normalized ratio with concomitant use of CBD or recreational cannabis.[82] Recommendations include regular monitoring of international normalized ratio in the presence of CBD or medical cannabis use and discouraging recreational cannabis use by patients taking warfarin.[83,84]

Cannabis acts as a CYP3A4 inhibitor, potentially resulting in increased circulating levels of buprenorphine and its metabolites. A retrospective analysis of 32 patients reported concentrations of buprenorphine 170% higher for those who consume recreational cannabis concomitant with buprenorphine.[85] Two case reports and 1 clinical trial reported increases of 358%, 200%, and 77% in the plasma level of tacrolimus with concomitant use of CBD.[86] Cannabis smoking induces CYP1A2 activity.[87] In 1 case report, plasma levels of clozapine increased by 230% after a patient stopped using cannabis and tobacco, and the patient experienced hallucinations.[88] Cannabis may increase methadone concentrations, possibly by inhibiting hepatic enzymes responsible for its metabolism. In 1 case report, methadone concentration increased by 117%, and somnolence and fatigue were reported in a patient using CBD oil.[89] Patients using these medications should avoid using cannabis products. Otherwise, clinicians should consider closely monitoring drug concentrations or adjusting doses of prescription medications to avoid potential toxicity. In 3 clinical trials of CBD oil used to treat refractory seizures, clobazam concentration was increased in patients receiving various doses of clobazam and CBD oil, leading to somnolence.[80,90] Recommendations include adjusting clobazam

dosage and, if it is possible, monitoring plasma levels.[91,92]

Modes of Administration and Pharmacokinetic Considerations

In general, there are 4 typical routes of administration for medical cannabis, with widely varying pharmacokinetic properties that influence each formulation's onset and duration of action (Table 1).[93] Inhaled, orally ingested, and topical or transdermal preparations are the primary delivery routes for CB therapies. The absorption, distribution, and metabolism of each formulation and dosage determine the onset and duration of action of cannabis products.[94] Of these, absorption is the most variable due to the highly lipophilic nature of CBs and the different organ systems involved in consumption.[93,94]

Pulmonary

Inhalation is a highly favored route of administration, with 86.6% of cannabis users in 1 international survey indicating a preference for this method.[93] Absorption of THC is rapid when inhaled, reaching mean peak concentrations at 6-10 minutes after smoking, with bioavailability ranging from 10% to 35%.[95] Inhaled THC reaches maximum physiologic effect within 15-30 minutes, then reduces gradually over 2-3 hours.[96]

It is essential to differentiate between the effects of smoking versus vaporizing cannabis. Smoking involves heating cannabis flower using combustion, converting the acidic form of THC into the active form via decarboxylation.[94] This process generates combustion by-products, carcinogens, and carbon monoxide, which can contribute to respiratory irritation, coughing, and bronchitis when used chronically.[97] Cancer and chronic obstructive pulmonary disease risk does not appear to be elevated in people who smoke only cannabis but may be elevated in people who combine tobacco and cannabis smoking.[98]

The process of heating and inhaling dried cannabis flower or cannabis oils using a noncombustive device is known as vaporizing, or "vaping." When dried cannabis flower is vaporized and inhaled, there is reduced production of combustion by-products, resulting in reduced respiratory irritation. This is seen as a more favorable method of consuming inhaled cannabis flower.[99,100] The term *vaping* also refers to heating and inhaling concentrated cannabis oils using a portable cartridge and battery.[101] In contrast to cannabis flower, these oils are highly concentrated with THC (70%-90%) and can contain additives and contaminants due to lack of regulation.[102] In 2019, THC-containing vape cartridges were associated with an outbreak of lung disease due to vitamin E acetate, which is toxic when inhaled.[103,104]

Oral

While inhaled cannabis may be popular among users overall (medical and nonmedical), orally administered preparations are commonly used by patients. This method of administration remains the most unpredictable in terms of dosing and effects. Ingested cannabinoids take 1-6 hours to reach maximal plasma THC concentrations, with bioavailability ranging from 4% to 12%.[94] When taken orally, THC is absorbed through the gastrointestinal tract and transported to the liver, where it is metabolized into 11-OH-THC, a potent metabolite with increased psychoactivity. A second metabolite, 11-COOH-THC, which is not psychoactive, is stored in the lipid tissues for 30-90 days and gradually excreted in the urine.[105] The onset of physiologic effects from orally ingested cannabis takes place over 2-3 hours, with effects lasting 4-12 hours.[96] The plasma half-life of THC appears to be biphasic, with an initial half-life of about 4 hours, followed by additional metabolism over 1-3 days.[106] CBD is also highly lipophilic, with an oral bioavailability of 6%. It is rapidly distributed in the body and has an elimination half-life of 1-32 hours.[107]

Oromucosal

Oromucosal cannabis preparations are gaining popularity as an alternative to smoking or oral ingestion. Nabiximols is an oromucosal formulation developed for the treatment of pain and spasticity in patients with multiple sclerosis.[108] The oral mucosa facilitates direct absorption of cannabinoids into the bloodstream, bypassing the hepatic first-pass effect and resulting in a more rapid onset of action.[94] In Phase I studies of high THC formulations and balanced formulations with equal parts THC:CBD, traces of both formulations were detectible in blood within 30-45 minutes of administration, with an estimated bioavailability of 11%-13%.[109] One limitation of the oromucosal route is the requirement of the presence of a moderate amount of saliva for successful absorption. Oromucosal cannabis preparations have significant therapeutic potential due to their more rapid onset and simple dosing. Nabiximols is currently available in Europe and Canada, with US FDA approval pending.

Topical and Transdermal

Topical cannabinoid preparations have therapeutic interest due to their anti-inflammatory, antioxidative, antiacne, anti-UVA/UVB damage, and antimicrobial properties in multiple studies.[110,111] When applied topically, cannabis preparations exert their effects by targeting the components of the ECS in the skin,

including epidermal keratinocytes, cutaneous nerve fibers, dermal cells, melanocytes, eccrine sweat glands, and hair follicles.[112] By interacting with numerous receptors, including CB1, CB2, peroxisome proliferator-activated nuclear receptors, and TRP channels, cannabinoids modulate vital processes to support the skin barrier, including anti-inflammatory, analgesic, and neuroprotective cellular effects.[113] Cannabis-based topical compounds have been helpful in the treatment of seborrheic keratitis, psoriasis, eczema, skin cancer, and pruritus.[111,114–116] There are increasing reports of successful treatment of various skin conditions using THC and CBD topical preparations.[117] Another area of therapeutic promise for topical cannabinoids is wound healing. Multiple components of the skin ECS, including CB receptors, cytokines, and TRP channels, influence wound healing.[118] A recent small study of a topical CBD preparation in addition to compression dressings for complex venous leg ulcers resulted in complete wound healing in 79% of the patients and 81% of the wounds after 34 days.[119]

Transdermal drug delivery (TDD) targets systemic circulation and aims to provide systemic dosing and steady therapeutic plasma drug levels. The highly lipophilic nature of CBs is advantageous in the realm of TDD and can provide an effective alternative to the low bioavailability of the oral route.[120] The dermal route is attractive because it allows a steadier infusion of CBs over a more extended time period.[113] Transdermal patches can provide systemic delivery of cannabinoids for symptom relief when methods like smoking or oral ingestion are not an option, such as in patients with cancer experiencing nausea and vomiting while undergoing chemotherapy.[121] Optimizing skin permeability and absorption of CBs is a significant focus of research, with interest in liposomes, nanoparticles, and microneedles as examples of common permeability enhancers being explored with transdermal preparations.[122,123] Topical and transdermal cannabis preparations hold great therapeutic promise due to their local applications, avoidance of hepatic first-pass metabolism, and steady drug delivery. Further focused studies are needed to optimize TDD systems and standardize formulations.

Dosing and Administration

Due to a lack of traditional double-blind RCTs for guidance, there are limited disease- or condition-specific dosing or formulation recommendations for medical cannabis products. Several recent publications of expert guidelines provide generalized dosing, titration, and monitoring recommendations for medical cannabis products. Current recommendations are based mainly on pharmacokinetics and observational studies, with data from pharmaceutical studies where applicable.[124]

For inhaled or vaporized cannabis, recommendations are limited. This is due to the wide variety of cannabis flower potency, CB content, and individual patient inhalation styles. There are thousands of cannabis chemovars (strains) available to patients, with highly variable potency and CB content.[125] THC potency in cannabis flower has risen from 8.9% in 2008 up to 17.1% in 2017.[126] Recently, cannabis flower types have been categorized relative to their proportions of THC:CBD, making broad recommendations possible. Type 1 cannabis is rich in THC, with low proportions of CBD. This cannabis is the predominant type sold in dispensaries across North America and consumed recreationally. Type II cannabis has a balanced proportion of THC:CBD and is of greater interest and medicinal usefulness due to its reduced impairing properties and efficacy in pharmaceutical studies. Type III cannabis contains high proportions of CBD with low amounts of THC. Type III cannabis is considered ideal for initiating medical cannabis due to its low risk of impairment and tolerability.[127,128] From a clinical perspective, inhaled cannabis use is often discouraged due to respiratory symptom concerns and inconsistent dosing, but it remains a highly popular method of consumption and may be beneficial for some patients in whom a rapid onset of action is desired (eg, breakthrough cancer pain). Counseling and harm reduction strategies include advising patients on using minimum effective dosing, with the strategic phrase "start low, go slow, and stay low."[93,124] A proposed strategy for dosing would be to take 1 inhalation and wait 15 minutes to observe the effects, with repeated doses of 1 inhalation every 15-30 minutes until relief is achieved.[93]

Oral Dosing

Much of the evidence and guidance for medical cannabis dosing is focused on oral and mucosal formulations. Initial dosing recommendations can be derived from clinical studies of several cannabinoid-based pharmaceutical preparations that have been approved by the FDA. In the United States, these FDA-approved medications include dronabinol and nabilone, which are synthetic THC formulations approved for cancer, chemotherapy, and HIV-related nausea, vomiting, and cachexia,[129,130] and a purified botanical CBD preparation approved for pediatric seizure disorders.[131] Outside of the United States, nabiximols is a botanically derived THC:CBD preparation approved as an oromucosal spray for pain and spasticity related to multiple sclerosis.[108,109] Dosing strategies for oral cannabis preparations should seek to optimize the analgesic,

Table 3. Proposed Oral Cannabis Dosing and Titration[124]

	Routine protocol	Conservative protocol	Rapid protocol
Initial cannabis type	CBD dominant (Type III)	Balanced THC:CBD (Type II)	
Initial dose	CBD 5 mg 1-2 times daily		2.5-5 mg each of THC and CBD 1-2 times daily
Initial titration	Increase CBD daily dose by 10 mg every 2-3 days		Increase THC and CBD daily doses each by 2.5 mg every 2–3 days
When to add THC	If treatment goals not met at CBD dose >40 mg/day		
Starting dose of THC	2.5 mg THC daily	1 mg THC daily	
Continued titration	Increase THC daily dose by 2.5 mg every 7 days	Increase THC daily dose by 1 mg every 7 days	
Consider discontinuing cannabis	If treatment goals not met at THC dose >40 mg/day, or if adverse effects exceed benefit		If treatment goals not met at THC and CBD doses >40 mg/day, or if adverse effects exceed benefits

CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol.

antispasmodic, and anxiolytic properties of cannabis while minimizing psychoactivity and impairment risks.

A 2022 consensus recommendation from an international panel of experts has proposed a series of protocols for initiating and titrating oral cannabis formulations for general symptom relief. The initial products and dosing should be CBD dominant, with a starting dosage of 5 mg CBD once or twice daily. Once the CBD dose exceeds 40 mg daily, and if symptoms remain persistent, adding THC can be considered. The initial dose of recommended THC is 1-2.5 mg/day. Titration may continue until symptoms are relieved or there is impairment, with a maximum THC dose of 40 mg daily.[93,124] An example titration protocol is included below (Table 3). Daily high-dose THC use of greater than 20-40 mg should prompt further screening for tolerance or misuse.[93,124]

Monitoring

Following the initiation of medical cannabis products, patients must be monitored for symptom response, impairment, and adverse effects. In studies examining lethal dosing following oral administration, the median lethal dose of THC is 800 mg/kg in rats, 3000 mg/kg in dogs, and up to 9000 mg/kg in monkeys.[124] A lethal THC dose for a 70-kg human is estimated at approximately 4000 mg/kg (280,000 mg THC), which is unlikely to be achieved using standard consumption methods.[132] THC alone does not cause cardiorespiratory suppression and fatal overdose due to a lack of CB receptors in the central respiratory centers and brain stem.[133] Additionally, patients tend to develop tolerance for the psychoactive effects of THC without developing tolerance to the therapeutic effects on pain, anxiety, and sleep.[134] Once patients achieve the desired symptom relief, many can maintain stable doses for years.

The most commonly reported side effects of cannabis-based medications include drowsiness, dry mouth, dizziness, cognitive effects, and respiratory symptoms if smoking.[135] Dose-dependent adverse effects tend to increase with higher amounts of THC, including blurred vision, orthostatic hypotension, ataxia, tachycardia, diarrhea, nausea, and psychosis.[136] One concerning effect is the development of cannabis hyperemesis syndrome, a cyclic vomiting condition that may lead to dehydration, electrolyte imbalance, and hospitalization. This appears to be increasing among younger, regular users of high-potency THC products and can be very debilitating.[137] The risk of adverse effects increases with higher THC doses, so the recommended approach to harm reduction, counseling, and monitoring is to advise using CBD-rich cannabis products, with low daily THC dosing, avoiding high-potency cannabis use.

Monitoring is imperative during the first weeks of initiation and titration of medical cannabis products. Follow-up visits should correlate with the patient's degree of cannabis experience and active titration of products. During the early phases of using medical cannabis, biweekly or monthly follow-up is appropriate; however once symptoms and dosing are stable, monitoring can be less frequent, based on individualized patient need and regulatory requirements. An essential part of monitoring patients using medical cannabis is deciding when it may be appropriate to discontinue use. In general, if a patient has reached maximal recommended dosages of THC (ie, greater than 40 mg) without relief or has persistent impairment, symptom worsening, or signs of a CUD, a recommendation should be made to discontinue cannabis.[124] Keeping track of symptoms using a journal may help patients monitor their individual responses to cannabis formulations.[93,124]

Summary

Although most currently practicing health care providers in the United States. have not received formal training related to the pharmaceutical and clinical science of the cannabis plant, patients increasingly wish to discuss CBs as a therapeutic option. Understanding the pharmacology of the cannabis plant and the evidence base for cannabis-based medicines may help providers feel more confident discussing these topics with patients. The standard of care for medical cannabis should be no different than any other specialty of medical care. A bona fide patient–provider relationship, a thorough review of medical records, medications, and history, along with a comprehensive physical examination, documentation, and effective communication with clinicians and caregivers, are all essential components of caring for patients using medical cannabis.

Conflicts of Interest

The author declares no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability Statement

The author has provided the required Data Availability Statement, and if applicable, included functional and accurate links to said data therein.

References

1. Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. *Chem Biodivers*. 2007;4(8):1614-1648. https://doi.org/10.1002/cbdv.200790144 PMID: 17712811
2. Pisanti S, Bifulco M. Modern history of medical cannabis: from widespread use to prohibitionism and back. *Trends Pharmacol Sci*. 2017;38(3):195-198. https://doi.org/10.1016/j.tips.2016.12.002
3. Zeese KB. History of medical marijuana policy in US. *Int J Drug Policy*. 1999;10:319-328. Accessed October 1, 2023. www.csdp.org
4. Silver RJ. The endocannabinoid system of animals. *Animals*. 2019;9(9). https://doi.org/10.3390/ANI9090686
5. Behl T, Makkar R, Sehgal A, et al. Exploration of multiverse activities of endocannabinoids in biological systems. *Int J Mol Sci*. 2022;23(10). https://doi.org/10.3390/ijms23105734
6. Chanda D, Neumann D, Glatz JFC. The endocannabinoid system: overview of an emerging multi-faceted therapeutic target. *Prostaglandins Leukot Essent Fatty Acids*. 2019;140:51-56. https://doi.org/10.1016/j.plefa.2018.11.016
7. Di Marzo V, Piscitelli F. The endocannabinoid system and its modulation by phytocannabinoids. *Neurotherapeutics*. 2015;12(4):692-698. https://doi.org/10.1007/s13311-015-0374-6
8. Oyagawa CRM, Grimsey NL. Cannabinoid receptor CB1 and CB2 interacting proteins: techniques, progress and perspectives. *Methods Cell Biol*. 2021;166:83-132. https://doi.org/10.1016/bs.mcb.2021.06.011
9. Rezende B, Alencar AKN, de Bem GF, Fontes-Dantas FL, Montes GC. Endocannabinoid system: chemical characteristics and biological activity. *Pharmaceuticals*. 2023;16(2). https://doi.org/10.3390/ph16020148
10. Brunt TM, Bossong MG. The neuropharmacology of cannabinoid receptor ligands in central signaling pathways. *Eur J Neurosci*. 2022;55(4):909-921. https://doi.org/10.1111/ejn.14982
11. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacol Rev*. 2010;62(4):588-631. https://doi.org/10.1124/pr.110.003004
12. Davis MP. Overview of the Endocannabinoid system and endocannabinoidome. In: *Cannabis and Cannabinoid-Based Medicines in Cancer Care*. Springer International Publishing; 2022:1-40. https://doi.org/10.1007/978-3-030-89918-9_1
13. National Academies of Sciences Engineering and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. The National Academies Press; 2017. https://doi.org/10.17226/24625
14. Piomelli D, Russo EB. The *Cannabis sativa* versus *Cannabis indica* debate: an interview with Ethan Russo, MD. *Cannabis Cannabinoid Res*. 2016;1(1):44-46. https://doi.org/10.1089/can.2015.29003.ebr
15. Pollio A. The name of cannabis: a short guide for nonbotanists. *Cannabis Cannabinoid Res*. 2016;1(1):234-238. https://doi.org/10.1089/can.2016.0027
16. Birenboim M, Chalupowicz D, Maurer D, et al. Multivariate classification of cannabis chemovars based on their terpene and cannabinoid profiles. *Phytochemistry*. 2022;200:113215. https://doi.org/10.1016/j.phytochem.2022.113215
17. Gülck T, Møller BL. Phytocannabinoids: origins and biosynthesis. *Trends Plant Sci*. 2020;25(10):985-1004. https://doi.org/10.1016/j.tplants.2020.05.005
18. Schilling S, Melzer R, Mccabe PF. Current biology of *Cannabis sativa*. *Curr Biol*. 2019;30:R8-R9. https://doi.org/10.1101/458083 bioRxiv
19. Andre CM, Hausman JF, Guerriero G. *Cannabis sativa*: the plant of the thousand and one molecules. *Front Plant Sci*. 2016;7(FEB2016). https://doi.org/10.3389/fpls.2016.00019
20. Bonini SA, Premoli M, Tambaro S, et al. *Cannabis sativa*: a comprehensive ethnopharmacological review of a medicinal plant with a long history. *J Ethnopharmacol*. 2018;227:300-315. https://doi.org/10.1016/j.jep.2018.09.004
21. Pertwee RG. The diverse CB 1 and CB 2 receptor pharmacology of three plant cannabinoids: Δ 9-tetrahydrocannabinol, cannabidiol and Δ 9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153(2):199-215. https://doi.org/10.1038/sj.bjp.0707442
22. Frye P, Smitherman D. *The Medical Marijuana Guide: Cannabis and Your Health*. Rowman & Littlefield Publishers; 2018.
23. Freeman TP, Craft S, Wilson J, et al. Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. *Addiction*. 2021;116(5):1000-1010. https://doi.org/10.1111/add.15253
24. Schoeler T, Ferris J, Winstock AR. Rates and correlates of cannabis-associated psychotic symptoms in over 230,000 people who use cannabis. *Transl Psychiatry*. 2022;12(1). https://doi.org/10.1038/s41398-022-02112-8
25. O'Sullivan SE, Jensen SS, Nikolajsen GN, Bruun HZ, Bhuller R, Hoeng J. The therapeutic potential of purified cannabidiol. *J Cannabis Res*. 2023;5(1):21. PMID: 37312194; PMCID: PMC10262148. https://doi.org/10.1186/s42238-023-00186-9

26. Englund A, Oliver D, Chesney E, et al. Does cannabidiol make cannabis safer? A randomised, double-blind, cross-over trial of cannabis with four different CBD:THC ratios. *Neuropsychopharmacology*. 2023;48(6):869-876. https://doi.org/10.1038/s41386-022-01478-z
27. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163:1344-1364. https://doi.org/10.1111/bph.2011.163.issue-7
28. Hanuš LO, Hod Y. Terpenes/terpenoids in cannabis: are they important? *Med Cannabis Cannabinoids*. 2020;3(1):61-73. https://doi.org/10.1159/000509733
29. Rose JE, Behrnapb FM. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. *Drug Alcohol Depend*. 1994;34(3):225-229. https://doi.org/10.1016/0376-8716(94)90160-0
30. Simei JLQ, Souza JDR, Lisboa JR, et al. Does the "entourage effect" in cannabinoids exist? A narrative scoping review. *Cannabis Cannabinoid Res*. Published online August 3, 2023. https://doi.org/10.1089/can.2023.0052
31. Santiago M, Sachdev S, Arnold JC, Mcgregor IS, Connor M. Absence of entourage: terpenoids commonly found in cannabis sativa do not modulate the functional activity of Δ9-THC at human CB1 and CB2 receptors. *Cannabis Cannabinoid Res*. 2019;4(3):165-176. https://doi.org/10.1089/can.2019.0016
32. Heblinski M, Santiago M, Fletcher C, et al. Terpenoids commonly found in cannabis sativa do not modulate the actions of phytocannabinoids or endocannabinoids on TRPA1 and TRPV1 channels. *Cannabis Cannabinoid Res*. 2020;5(4):305-317. Published 2020 Dec 15. https://doi.org/10.1089/can.2019.0099
33. Schlag AK, O'Sullivan SE, Zafar RR, Nutt DJ. Current controversies in medical cannabis: recent developments in human clinical applications and potential therapeutics. *Neuropharmacology*. 2021;191. https://doi.org/10.1016/j.neuropharm.2021.108586
34. National Conference of State Legislatures. State Medical Cannabis Laws. Published June 22, 2023. Accessed September 3, 2023. https://www.ncsl.org/health/state-medical-cannabis-laws
35. DEA. Drug Scheduling. Published July 10, 2018. Accessed September 3, 2023. https://www.dea.gov/drug-information/drug-scheduling
36. Boehnke KF, Dean O, Haffajee RL, Hosanagar A. U.S. trends in registration for medical cannabis and reasons for use from 2016 to 2020: an observational study. *Ann Intern Med*. 2022;175(7):945-951. https://doi.org/10.7326/M22-0217
37. Azcarate PM, Zhang AJ, Keyhani S, Steigerwald S, Ishida JH, Cohen BE. Medical reasons for marijuana use, forms of use, and patient perception of physician attitudes among the US population. *J Gen Intern Med*. 2020;35(7):1979-1986. https://doi.org/10.1007/s11606-020-05800-7
38. Hall A. CBD Statistics, Data And Use (2023) – Forbes Health. Published July 10, 2023. Accessed September 3, 2023. https://www.forbes.com/health/body/cbd-statistics/
39. Burston JJ, Woodhams SG. Endocannabinoid system and pain: an introduction. *Proc Nutr Soc*. 2014;73(1):106-117. https://doi.org/10.1017/S0029665113003650
40. Guindon J, Hohmann AG, Program B. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets*. 2009;8(6):403-421.
41. McDonagh MS, Morasco BJ, Wagner J, Ahmed AY, Fu R, Kansagara D, Chou R. Cannabis-based products for chronic pain: a systematic review. *Ann Intern Med*. 2022;175(8):1143-1153. https://doi.org/10.7326/M21-4520.
42. Dowell D, Ragan K, Jones C, Baldwin G, Chou R. CDC clinical practice guideline for prescribing opioids for pain — United States, 2022. *MMWR Recomm Rep*. 2022;71(RR-3):1-95. https://doi.org/10.15585/mmwr.rr7103a1
43. Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open*. 2021;11:47717. https://doi.org/10.1136/bmjopen-2020-047717
44. Hasbi A, Madras BK, George SR. Endocannabinoid system and exogenous cannabinoids in depression and anxiety: a review. *Brain Sci*. 2023;13(2). https://doi.org/10.3390/brainsci13020325
45. Viveros MP, Marco EM, File SE. Endocannabinoid system and stress and anxiety responses. *Pharmacol Biochem Behav*. 2005;81(2):331-342. https://doi.org/10.1016/j.pbb.2005.01.029
46. Stanciu CN, Brunette MF, Teja N, Budney AJ. Evidence for use of cannabinoids in mood disorders, anxiety disorders, and PTSD: a systematic review. *Psychiatr Serv*. 2021;72(4):429. https://doi.org/10.1176/APPI.PS.202000189
47. Fabre LF, McLendon D. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. *J Clin Pharmacol*. 1981;21(S1):377S-382S. https://doi.org/10.1002/j.1552-4604.1981.tb02617.x
48. Bergamaschi MM, Queiroz RHC, Chagas MHN, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219-1226. https://doi.org/10.1038/NPP.2011.6
49. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. *Front Psychol*. 2019;10:2466. https://doi.org/10.3389/FPSYG.2019.02466
50. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473. https://doi.org/10.1001/JAMA.2015.6358
51. Kesner AJ, Lovinger DM. Cannabinoids, endocannabinoids and sleep. *Front Mol Neurosci*. 2020;13. https://doi.org/10.3389/fnmol.2020.00125
52. Velzeboer R, Malas A, Boerkoel P, Cullen K, Roesler J, Wei-Ku Lai W. Cannabis dosing and administration for sleep: a systematic review [published correction appears in Sleep. 2023 Mar 9;46(3):]. Sleep. 2022;45(11):zsac218. https://doi.org/10.1093/sleep/zsac218
53. Miranda A, Peek E, Ancoli-Israel S, Young JW, Perry W, Minassian A. The role of cannabis and the endocannabinoid system in sleep regulation and cognition: a review of human and animal studies. *Behav Sleep Med*. Published online July 3, 2023. https://doi.org/10.1080/15402002.2023.2232497
54. Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. Endocannabinoid system and mood disorders: priming a target for new therapies. *Pharmacol Ther*. 2013;138:18-37. https://doi.org/10.1016/j.pharmthera.2012.12.002
55. Jefsen OH, Erlangsen A, Nordentoft M, Hjorthøj C. Cannabis use disorder and subsequent risk of psychotic and nonpsychotic unipolar depression and bipolar disorder. *JAMA Psychiatry*. 2023;80(8):803-810. https://doi.org/10.1001/jamapsychiatry.2023.1256
56. Sam AH, Salem V, Ghatei MA. Rimonabant: from RIO to ban. *J Obes*. 2011;2011:432607. https://doi.org/10.1155/2011/432607
57. Sarris J, Sinclair J, Karamacoska D, Davidson M, Firth J. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. *BMC Psychiatry*. 2020;20(1):24.

Published 2020 Jan 16. https://doi.org/10.1186/s12888-019-2409-8
58. Philpot LM, Ebbert JO, Hurt RT. A survey of the attitudes, beliefs and knowledge about medical cannabis among primary care providers. *BMC Fam Pract*. 2019;20(1):17. https://doi.org/10.1186/s12875-019-0906-y
59. Abo Ziad R, Grynbaum MB, Peleg R, Treister-Goltzman Y. The attitudes and beliefs of family physicians regarding the use of medical cannabis, knowledge of side effects, and barriers to use: a comparison between residents and specialists. *Am J Ther*. 2022;29(4):e400-e409. https://doi.org/10.1097/MJT.0000000000001236
60. Ryan JE, McCabe SE, Boyd CJ. Medicinal cannabis: policy, patients, and providers. *Policy Polit Nurs Pract*. 2021;22(2):126-133. https://doi.org/10.1177/1527154421989609
61. SAMHSA. NSDUH Report SAMHSA 2021. Published 2021. Accessed October 2, 2023. https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report
62. Gregorio J. Physicians, medical marijuana, and the law. *AMA J Ethics*. 2014;16(9):732-738. https://doi.org/10.1001/virtualmentor.2014.16.9.hlaw1-1409
63. Connor JP, Stjepanović D, Le Foll B, Hoch E, Budney AJ, Hall WD. Cannabis use and cannabis use disorder. *Nat Rev Dis Primers*. 2021;7(1):16. https://doi.org/10.1038/s41572-021-00247-4
64. Connor JP, Stjepanović D, Budney AJ, Le Foll B, Hall WD. Clinical management of cannabis withdrawal. *Addiction*. 2022;117(7):2075-2095. https://doi.org/10.1111/add.15743
65. Petrilli K, Ofori S, Hines L, Taylor G, Adams S, Freeman TP. Association of cannabis potency with mental ill health and addiction: a systematic review. *Lancet Psychiatry*. 2022;9(9):736-750. https://doi.org/10.1016/S2215-0366(22)00161-4
66. Robinson T, Ali MU, Easterbrook B, et al. Identifying risk-thresholds for the association between frequency of cannabis use and development of cannabis use disorder: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2022;238:109582. https://doi.org/10.1016/j.drugalcdep.2022.109582
67. Carvalho C, Vieira-Coelho MA. Cannabis induced psychosis: a systematic review on the role of genetic polymorphisms. *Pharmacol Res*. 2022;181:106258. https://doi.org/10.1016/j.phrs.2022.106258
68. Schoeler T, Ferris J, Winstock AR. Rates and correlates of cannabis-associated psychotic symptoms in over 230,000 people who use cannabis. *Transl Psychiatry*. 2022;12(1):369. https://doi.org/10.1038/s41398-022-02112-8
69. Forti D, Marconi A, Carra E, et al. Proportion of patients in south London with fi rst-episode psychosis attributable to use of high potency cannabis: a case-control study. *Articles Lancet Psychiatry*. 2015;2:233-271. https://doi.org/10.1016/S2215-0366(14)00117-5
70. Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*. 2016;15(3):195-204. https://doi.org/10.1002/wps.20341
71. Lo JO, Shaw B, Robalino S, et al. Cannabis use in pregnancy and neonatal outcomes: a systematic review and meta-analysis. *Cannabis Cannabinoid Res*. Published online February 1, 2023. https://doi.org/10.1089/can.2022.0262
72. Baía I, Domingues RMSM. The effects of cannabis use during pregnancy on low birth weight and preterm birth: a systematic review and meta-analysis. *Am J Perinatol*. 2024;41(1):17-30. https://doi.org/10.1055/a-1911-3326
73. Abrams RM, Cook CE, Davis KH, Niederreither K, Jaeger MJ, Szeto HH. Plasma delta-9-tetrahydrocannabinol in pregnant sheep and fetus after inhalation of smoke from a marijuana cigarette. *Alcohol Drug Res*. 1985;6:361–369.
74. Berghuis P, Rajnicek AM, Morozov YM, et al. Hardwiring the brain: endocannabinoids shape neuronal connectivity. *Science (1979)*. 2007;316(5828):1212-1216. https://doi.org/10.1126/science.1137406
75. Cristino L, Di Marzo V. Fetal cannabinoid receptors and the "dis-joint-ed" brain. *EMBO J*. 2014;33(7):665-667. https://doi.org/10.1002/embj.201488086
76. Dahl RE. A longitudinal study of prenatal marijuana use. *Arch Pediatr Adolesc Med*. 1995;149(2):145. https://doi.org/10.1001/archpedi.1995.02170140027004
77. Fried PA, Watkinson B, Siegel LS. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 1997;19(3):171-183. https://doi.org/10.1016/S0892-0362(97)00015-9
78. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 1998;20(3):293-306. https://doi.org/10.1016/S0892-0362(97)00091-3
79. American College of Obstetrics and Gynecology. Marijuana use during pregnancy and lactation. Committee Opinion No. 722. *Obstet Gynecol*. 2017;130(4):205-209.
80. Lopera V, Rodríguez A, Amariles P. Clinical relevance of drug interactions with cannabis: a systematic review. *J Clin Med*. 2022;11(5):1154. https://doi.org/10.3390/jcm11051154
81. Alsherbiny M, Li C. Medicinal cannabis—potential drug interactions. *Medicines*. 2018;6(1):3. https://doi.org/10.3390/medicines6010003
82. Damkier P, Lassen D, Christensen MMH, Madsen KG, Hellfritzsch M, Pottegård A. Interaction between warfarin and cannabis. *Basic Clin Pharmacol Toxicol*. 2019;124(1):28-31. https://doi.org/10.1111/bcpt.13152
83. Hsu A, Painter NA. Probable interaction between warfarin and inhaled and oral administration of cannabis. *J Pharm Pract*. 2020;33(6):915-918. https://doi.org/10.1177/0897190019854958
84. Yamreudeewong W, Wong HK, Brausch LM, Pulley KR. Probable interaction between warfarin and marijuana smoking. *Ann Pharmacother*. 2009;43(7-8):1347-1353. https://doi.org/10.1345/aph.1M064
85. Vierke C, Marxen B, Boettcher M, Hiemke C, Havemann-Reinecke U. Buprenorphine–cannabis interaction in patients undergoing opioid maintenance therapy. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(5):847-856. https://doi.org/10.1007/s00406-019-01091-0
86. Leino AD, Emoto C, Fukuda T, Privitera M, Vinks AA, Alloway RR. Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus. *Am J Transplant*. 2019;19(10):2944-2948. https://doi.org/10.1111/ajt.15398
87. Anderson GD, Chan LN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. *Clin Pharmacokinet*. 2016;55. https://doi.org/10.1007/s40262-016-0400-9
88. Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int Clin Psychopharmacol*. 2002;17(3):141-143. https://doi.org/10.1097/00004850-200205000-00008

89. Madden K, Tanco K, Bruera E. Clinically significant drug-drug interaction between methadone and cannabidiol. *Pediatrics*. 2020;145(6):e20193256. https://doi.org/10.1542/peds.2019-3256
90. Chesney E, Oliver D, Green A, et al. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. *Neuropsychopharmacology*. 2020;45(11):1799-1806. https://doi.org/10.1038/s41386-020-0667-2
91. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 2015;56(8):1246-1251. https://doi.org/10.1111/epi.13060
92. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia*. 2017;58(9):1586-1592. https://doi.org/10.1111/epi.13852
93. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med*. 2018;49:12-19. https://doi.org/10.1016/j.ejim.2018.01.004
94. Kebede L, Masoomi Dezfooli S, Seyfoddin A. Medicinal cannabis pharmacokinetics and potential methods of delivery. *Pharm Dev Technol*. 2022;27(2):202-214. https://doi.org/10.1080/10837450.2022.2035748
95. Chayasirisobhon S. Mechanisms of action and pharmacokinetics of cannabis. *Perm J*. 2021;25(1):1-3. https://doi.org/10.7812/TPP/19.200
96. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-360. https://doi.org/10.2165/00003088-200342040-00003
97. Joshi M, Joshi A, Bartter T. Marijuana and lung diseases. *Curr Opin Pulm Med*. 2014;20(2):173-179. https://doi.org/10.1097/MCP.0000000000000026
98. Tashkin DP. Effects of marijuana smoking on the lung. *Ann Am Thorac Soc*. 2013;10(3):239-247. https://doi.org/10.1513/AnnalsATS.201212-127FR
99. 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. https://doi.org/10.1038/sj.clpt.6100200
100. Meehan-Atrash J, Rahman I. Cannabis vaping: existing and emerging modalities, chemistry, and pulmonary toxicology. *Chem Res Toxicol*. 2021;34(10):2169-2179. https://doi.org/10.1021/acs.chemrestox.1c00290
101. Bonner E, Chang Y, Christie E, et al. The chemistry and toxicology of vaping. *Pharmacol Ther*. 2021;225:107837. https://doi.org/10.1016/j.pharmthera.2021.107837
102. Stefaniak AB, LeBouf RF, Ranpara AC, Leonard SS. Toxicology of flavoring- and cannabis-containing e-liquids used in electronic delivery systems. *Pharmacol Ther*. 2021;224:107838. https://doi.org/10.1016/j.pharmthera.2021.107838
103. Fedt A, Bhattarai S, Oelstrom MJ. Vaping-associated lung injury: a new cause of acute respiratory failure. *J Adolesc Health*. 2020;66(6):754-757. https://doi.org/10.1016/j.jadohealth.2020.03.019
104. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *N Engl J Med*. 2020;382(8):697-705. https://doi.org/10.1056/NEJMoa1916433
105. McGilveray IJ. Pharmacokinetics of cannabinoids. *Pain Res Manag*. 2005;10(suppl a):15A-22A. https://doi.org/10.1155/2005/242516
106. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4(8):1770-1804. https://doi.org/10.1002/cbdv.200790152
107. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol*. 2018;84(11):2477-2482. https://doi.org/10.1111/bcp.13710
108. Sastre-Garriga J, Vila C, Clissold S, Montalban X. THC and CBD oromucosal spray (Sativex ®) in the management of spasticity associated with multiple sclerosis. *Expert Rev Neurother*. 2011;11(5):627-637. https://doi.org/10.1586/ern.11.47
109. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex ®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol*. 2011;18(9):1122-1131. https://doi.org/10.1111/j.1468-1331.2010.03328.x
110. Gerasymchuk M, Robinson GI, Groves A, et al. Phytocannabinoids stimulate rejuvenation and prevent cellular senescence in human dermal fibroblasts. *Cells*. 2022;11(23):3939. https://doi.org/10.3390/cells11233939
111. Oláh A, Markovics A, Szabó-Papp J, et al. Differential effectiveness of selected non-psychotropic phytocannabinoids on human sebocyte functions implicates their introduction in dry/seborrhoeic skin and acne treatment. *Exp Dermatol*. 2016;25(9):701-707. https://doi.org/10.1111/exd.13042
112. Mounessa JS, Siegel JA, Dunnick CA, Dellavalle RP. The role of cannabinoids in dermatology. *J Am Acad Dermatol*. 2017;77(1):188-190. https://doi.org/10.1016/j.jaad.2017.02.056
113. Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E. Cannabidiol—transdermal delivery and anti-inflammatory effect in a murine model. *J Control Release*. 2003;93(3):377-387. https://doi.org/10.1016/j.jconrel.2003.09.001
114. Palmieri B, Laurino C, Vadalà M. A. A therapeutic effect of cbd-enriched ointment in inflammatory skin diseases and cutaneous scars. *Clin Ter*. 2019;170(2):e93-e99. https://doi.org/10.7417/CT.2019.2116
115. Morin CB, Raef HS, Elmariah SB. Neuropathic itch treated with oral cannabinoids: a case series. *JAAD Case Rep*. 2021;17:38-42. https://doi.org/10.1016/j.jdcr.2021.09.006
116. Laborada J, Cohen PR. Cutaneous squamous cell carcinoma and lichen simplex chronicus successfully treated with topical cannabinoid oil: a case report and summary of cannabinoids in dermatology. *Cureus*. 2022;14(4):e23850. Published 2022 Apr 5. https://doi.org/10.7759/cureus.23850
117. Baswan SM, Klosner AE, Glynn K, et al. Therapeutic potential of cannabidiol (cbd) for skin health and disorders. *Clin Cosmet Investig Dermatol*. 2020;13:927-942. https://doi.org/10.2147/CCID.S286411
118. Bort A, Alvarado-Vazquez PA, Moracho-Vilrriales C, et al. Effects of JWH015 in cytokine secretion in primary human keratinocytes and fibroblasts and its suitability for topical/transdermal delivery. *Mol Pain*. 2017;13:174480691668822. https://doi.org/10.1177/1744806916688220
119. Maida V, Shi RB, Fazzari FGT, Zomparelli L. Topical cannabis-based medicines – a novel adjuvant treatment for venous leg ulcers: an open-label trial. *Exp Dermatol*. 2021;30(9):1258-1267. https://doi.org/10.1111/exd.14395
120. Anselmo AC, Mitragotri S. An overview of clinical and commercial impact of drug delivery systems. *J Control Release*. 2014;190:15-28. https://doi.org/10.1016/j.jconrel.2014.03.053
121. Valiveti S, Hammell DC, Earles DC, Stinchcomb AL. Transdermal delivery of the synthetic cannabinoid WIN 55,212-2:

in vitro/in vivo correlation. *Pharm Res*. 2004;21(7):1137-1145. https://doi.org/10.1023/B:PHAM.0000032999.31948.2e
122. Tapfumaneyi P, Imran M, Mohammed Y, Roberts MS. Recent advances and future prospective of topical and transdermal delivery systems. *Front Drug Deliv*. 2022;2:957732. https://doi.org/10.3389/fddev.2022.957732
123. 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. https://doi.org/10.1016/J.JCONREL.2021.05.005
124. Bhaskar A, Bell A, Boivin M, et al. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *J Cannabis Res*. 2021;3(1):22. Published 2021 Jul 2. https://doi.org/10.1186/s42238-021-00073-1
125. Lewis M, Russo E, Smith K. Pharmacological foundations of cannabis chemovars. *Planta Med*. 2018;84(04):225-233. https://doi.org/10.1055/s-0043-122240
126. Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). *Eur Arch Psychiatry Clin Neurosci*. 2019;269(1):5-15. https://doi.org/10.1007/s00406-019-00983-5
127. Smith CJ, Vergara D, Keegan B, Jikomes N. The phytochemical diversity of commercial Cannabis in the United States. *PLoS One*. 2022;17(5):e0267498. https://doi.org/10.1371/journal.pone.0267498
128. Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A Phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects. *CNS Drugs*. 2018;32(11):1053-1067. https://doi.org/10.1007/s40263-018-0578-5
129. de Vries M, van Rijckevorsel DC, Wilder-Smith OH, van Goor H. Dronabinol and chronic pain: importance of mechanistic considerations. *Expert Opin Pharmacother*. 2014;15(11):1525-1534. https://doi.org/10.1517/14656566.2014.918102
130. Pagano C, Navarra G, Coppola L, Avilia G, Bifulco M, Laezza C. Cannabinoids: therapeutic use in clinical practice. *Int J Mol Sci*. 2022;23(6):3344. https://doi.org/10.3390/ijms23063344
131. Arzimanoglou A BUCJ. Epilepsy and cannabidiol: a guide to treatment. *Epileptic Disord*. Published online 2020:1-14.
132. World Health Organization. WHO expert committee on drug dependence. *World Health Organ Tech Rep Ser*. 2012;(973):1-26. PMID: 24547667.
133. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci*. 1990;87(5):1932-1936. https://doi.org/10.1073/pnas.87.5.1932
134. Ware MA, Wang T, Shapiro S, et al. Cannabis for the management of pain: assessment of safety study (COMPASS). *J Pain*. 2015;16(12):1233-1242. https://doi.org/10.1016/j.jpain.2015.07.014
135. Ware MA, Tawfik VL. Safety issues concerning the medical use of cannabis and cannabinoids. *Pain Res Manag*. 2005;10(suppl a):31A-37A. https://doi.org/10.1155/2005/312357
136. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *Can Med Assoc J*. 2008;178(13):1669-1678. https://doi.org/10.1503/cmaj.071178
137. Perisetti A. Cannabis hyperemesis syndrome: an update on the pathophysiology and management. *Ann Gastroenterol*. 2020;33(6):571-578. https://doi.org/10.20524/aog.2020.0528
138. Food and Drug Administration. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. 2018. Accessed October 16, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms
139. Abrams DI. The therapeutic effects of Cannabis and cannabinoids: an update from the National Academies of Sciences, Engineering and Medicine report. *Eur J Int Med*. 2018;49:7-11. https://doi.org/10.1016/j.ejim.2018.01.003