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Therapeutic Use of Cannabis and Cannabinoids
A Review

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IMPORTANCE Approximately 27% of adults in the US and Canada report having ever used cannabis for medical purposes. An estimated 10.5% of the US population reports using cannabidiol (CBD), a chemical compound extracted from cannabis that does not have psychoactive effects, for therapeutic purposes.

OBSERVATIONS Conditions for which cannabinoids have approval from the US Food and Drug Administration include HIV/AIDS–related anorexia, chemotherapy-induced nausea and vomiting, and certain pediatric seizure disorders. A meta-analysis of randomized clinical trials reported a small but significant reduction in nausea and vomiting from various causes (eg, chemotherapy, cancer) when comparing prescribed cannabinoids (eg, dronabinol, nabilone) with placebo or active comparators (eg, alizapride, chlorpromazine; standardized mean difference [SMD], −0.29 [95% CI, −0.39 to −0.18]). A meta-analysis of randomized clinical trials among patients with HIV/AIDS reported that cannabinoids had a moderate effect on increasing body weight compared with placebo (SMD, 0.57 [95% CI, 0.22 to 0.92]). Evidence-based guidelines do not recommend the use of inhaled or high-potency cannabis (≥10% or 10 mg Δ9-tetrahydrocannabinol [Δ9-THC]) for medical purposes. High-potency cannabis compared with low-potency cannabis use is associated with increased risk of psychotic symptoms (12.4% vs 7.1%) and generalized anxiety disorder (19.1% vs 11.6%). A meta-analysis of observational studies reported that 29% of individuals who used cannabis for medical purposes met criteria for cannabis use disorder. Daily inhaled cannabis use compared with nondaily use was associated with an increased risk of coronary heart disease (2.0% vs 0.9%), myocardial infarction (1.7% vs 1.3%), and stroke (2.6% vs 1.0%). Evidence from randomized clinical trials does not support the use of cannabis or cannabinoids for most conditions for which it is promoted, such as acute pain and insomnia. Before considering cannabis or cannabinoids for medical use, clinicians should consult applicable institutional, state, and national regulations; evaluate for drug-drug interactions; and assess for contraindications (eg, pregnancy) or conditions in which risks likely outweigh benefits (eg, schizophrenia or ischemic heart disease). For patients using cannabis or cannabinoids for treatment of medical conditions, clinicians should discuss harm reduction strategies, including avoiding concurrent use with alcohol or other central nervous system depressants such as benzodiazepines, using the lowest effective dose, and avoiding use when driving or operating machinery.

CONCLUSIONS AND RELEVANCE Evidence is insufficient for the use of cannabis or cannabinoids for most medical indications. Clear guidance from clinicians is essential to support safe, evidence-based decision-making. Clinicians should weigh benefits against risks when engaging patients in informed discussions about cannabis or cannabinoid use.

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The term *cannabis* broadly refers to products derived from the *Cannabis* genus plant, and cannabinoids refers to active compounds found in cannabis, including synthetic forms (see the Glossary of Terms **Table 1**). Cannabis contains many cannabinoids, including Δ9-tetrahydrocannabinol (Δ9-THC), which is a psychoactive compound that causes the high associated with cannabis, and cannabidiol (CBD), which is nonintoxicating. Other chemicals found in cannabis are terpenes, flavonoids, and more than 140 lesser-known cannabinoids such as Δ8-THC.[5,6]

Of 27 169 adults, aged 16-65 years, participating in a 2018 survey conducted in the US and Canada,[7] 27% reported lifetime use of cannabis or cannabinoids for medical purposes, including treatment of pain (53%), anxiety (52%), and insomnia (46%).[8] However, a 2021 systematic review[9] of 15 studies (n = 5068) reported that only 33% of clinicians globally were confident in their knowledge of cannabis or cannabinoids and 86% reported a need for more education in this area.[9-11]

This review builds on a 2019 JAMA Insights article,[12] presenting current evidence about the therapeutic use of cannabis and cannabinoids among adults, potential harms, and evidence-based clinical guidance, including pretreatment screening and addressing preexisting cannabis use in clinical settings, with consideration of both US and global contexts. Despite the accumulation of new studies, evidence is insufficient for the use of cannabis or cannabinoids for most medical conditions. (See **Box 1** for Frequently Asked Questions.)

Table 1. Glossary of Terms

Endocannabinoid system	
Endocannabinoid system	A signaling network in the body that includes cannabinoid receptors, primarily cannabinoid receptors types 1 (CB1) and 2 (CB2), endogenous ligands (endocannabinoids), and enzymes responsible for their synthesis and breakdown. The endocannabinoid system regulates bodily functions including pain, mood, appetite, memory, and immune function
CB1	A G protein–coupled receptor (a large family of cell-surface receptors that transmit signals inside the cell through interactions with G proteins after binding an activating molecule) in the endocannabinoid system is primarily located in the central nervous system, especially in the brain. CB1 mediates many of the psychoactive effects of Δ9-tetrahydrocannabinol (Δ9-THC) and plays a role in modulating pain, appetite, mood, and memory
CB2	A G protein–coupled receptor predominantly found in peripheral tissues, including immune cells, the gastrointestinal tract, and the spleen. CB2 is associated with anti-inflammatory and immunomodulatory effects and is less involved in the psychoactive effects of cannabis
Cannabis and plant-derived products	
Cannabis	The unprocessed or minimally processed products derived from the flowering parts of the plant genus *Cannabis*, including *Cannabis sativa*, *Cannabis indica*, and hybrids thereof. These products contain a complex mixture of biologically active compounds, including more than 100 phytocannabinoids, terpenes, and flavonoids and are often ingested via inhalation (eg, smoking, vaping, dabbing [defined below]), or ingesting orally (eg, edibles, teas). *Cannabis* is the preferred scientific and clinical term used in research and policy while other terms such as *marijuana* and *weed* are used colloquially
Recreational cannabis	The use of cannabis for nonmedical, psychoactive, or personal enjoyment purposes
Medical cannabis	The use of cannabis or cannabinoids to address medical conditions, ideally though not necessarily under the supervision of a licensed clinician. Products labeled as *medical* are not necessarily chemically distinct from recreational cannabis and may have comparable Δ9-THC concentrations[1]
High-potency cannabis	Cannabis products with high Δ9-THC content, typically defined as more than 10% THC by weight if inhaled, or 5 mg or more to 10 mg of Δ9-THC per serving if orally consumed.[2-4] The potency of cannabis is largely determined by percentage Δ9-THC as opposed to route of administration
Cannabis concentrates	Highly concentrated cannabis extracts produced using solvents (eg, butane) or mechanical methods (ie, techniques that physically separate the resin glands from the plant material). Product forms vary by consistency and extraction technique. Such concentrates may be referred to as *dabs*, *wax*, or *shatter*, based on product consistency and extraction method
Vaping	Inhalation of cannabinoids through heating (not combustion) of dried cannabis or concentrates. May reduce exposure to combustion-related toxins compared with smoking
Dabbing	A method of vaporizing and inhaling cannabis concentrates (eg, butane hash oil) using a specialized heated surface or rig. Often delivers high doses of Δ9-THC
Cannabinoids	
Cannabinoids	A class of chemical compounds that act on cannabinoid receptors in the body. They include phytocannabinoids (eg, Δ9-THC and cannabidiol [CBD], derived from the cannabis plant), endocannabinoids (produced naturally in the body, such as anandamide), and synthetic cannabinoids (laboratory-produced compounds with similar activity, such as nabilone)
Pharmaceutical-grade cannabinoids	Purified or synthetic isolated cannabinoids that are US Food and Drug Administration approved for the treatment of specific medical conditions and require a prescription from a licensed clinician
Δ9-tetrahydrocannabinol	A phytocannabinoid that has psychoactive properties through its actions on cannabinoid receptors
Δ8-tetrahydrocannabinol	A cannabinoid that is a structural analogue of Δ9-THC; it is a partial agonist at the CB1 receptor and produces similar psychoactive effects but with lower potency than Δ9-THC[5]
Cannabidiol	A cannabinoid that modulates multiple receptors; acts as a negative allosteric modulator of CB1 (ie, binds to a receptor not directly at the CB1 site but reduces the receptor's activity) and an agonist at 5-HT1A and TRPV1 receptors, contributing to potential anti-inflammatory and anxiolytic effects. CBD is not known to cause euphoria or acute intoxication
Cannabigerol	A cannabinoid that exhibits analgesic and anti-inflammatory properties, likely through an α-2 adrenergic receptor agonism, TRPV1 activation, and modulation of CB2 receptors[6]
Other plant constituents	
Terpenes	Noncannabinoid phytochemicals produced by the *C sativa* plant that contribute to the aromatic properties of cannabis
Flavonoids	Noncannabinoid phytochemicals produced by the *C sativa* plant that may contribute to the antioxidative and anti-inflammatory properties of cannabis
Market context	
Unregulated markets	Products obtained outside state-regulated dispensaries or pharmacies, including unlicensed dispensaries, online marketplaces, or black markets (eg, dark web)

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Box 1. Frequently Asked Questions About Cannabis

What is the difference between cannabis and cannabinoids?

Cannabis refers to the whole plant, including its dried flowers, leaves, and extracts, which contain a variety of biologically active compounds. Cannabinoids, such as Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are chemical constituents of the cannabis plant that interact with the body's endocannabinoid system to produce physiological effects. Some cannabinoids such as dronabinol and cannabidiol are available as US Food and Drug Administration (FDA)–approved medications for specific indications. In contrast to FDA-approved pharmaceutical cannabinoids, cannabis products sold through dispensaries remain federally illegal under the US Controlled Substances Act, although many states have enacted laws permitting their medical and/or nonmedical use.

What medical conditions are approved for cannabis or cannabinoid use?

The use of cannabinoids is FDA approved for chemotherapy-induced nausea and vomiting, anorexia in people with HIV/AIDs, seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis. Evidence is insufficient for the use of cannabis or cannabinoids for most medical indications.

What are the primary risks associated with cannabis or cannabinoid use?

FDA-approved cannabinoids such as dronabinol, nabilone, and cannabidiol can cause dizziness (reported by 8%-15% of patients in randomized clinical trials), dry mouth (5%-13%), and gastrointestinal symptoms such as diarrhea (9%-59%). High-potency cannabis products (≥10% THC), commonly found in dispensaries but not FDA-approved, have been associated with adverse effects including increased risk of anxiety (19.1% among people who use high-potency cannabis vs 11.6% among people who do not use high-potency cannabis), psychotic symptoms (12.4% vs 7.1%), and cannabis use disorder (20%-30% of individuals who use cannabis daily).

Methods

We searched PubMed for English-language observational studies, randomized clinical trials (RCTs), systematic reviews, clinical guidelines, and meta-analyses published from January 1, 2010, to September 15, 2025. We identified 2576 articles and prioritized the inclusion of studies with the largest and most recent samples based on relevance and topics covered, with preference given to RCTs when available. References were reviewed to identify additional relevant articles prior to search dates. A total of 124 studies were included, consisting of 21 clinical guidelines, 7 systematic reviews, 3 meta-analyses, 24 combined systematic review and meta-analyses, 10 RCTs, 17 nonsystematic reviews, 4 package labels, 30 observational studies, and 8 other studies (eg, case reports). For meta-analyses comparing treatments, we reported standardized mean differences (SMDs) for changes in symptom scores when available. When comparing treatments, SMDs of 0.2, 0.5, and 0.8 are usually considered small, medium, and large effects, respectively.

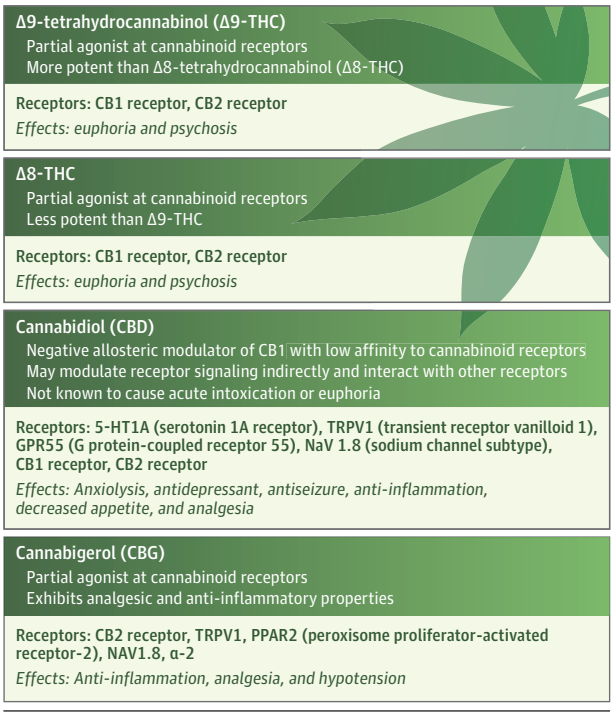
Discussion

Endocannabinoid System

Endocannabinoids, or cannabinoids naturally produced in the body, include anandamide and 2-arachidonoyl glycerol. These compounds act primarily on cannabinoid receptor types 1 (CB1) and 2 (CB2) that affect neurotransmitters, immune cell activity, metabolism, and stress response. CB1 receptors are abundant in the brain and are widely expressed in regions involved in cognition; emotion; and reward processing including the prefrontal cortex, hippocampus, and amygdala.[13] CB1 receptors are also expressed at lower levels in peripheral tissues, including the heart and vasculature, where activation by cannabinoids may lead to vasodilation and decreased myocardial contractility.[14] CB2 receptors, which are primarily found on immune cells and peripheral tissues, modulate inflammation and immune function.[15]

The endocannabinoid system can also be modulated by exogenous cannabinoids such as Δ9-THC and CBD. Δ9-THC acts as a partial agonist at CB1 receptors and is primarily responsible for the psychoactive effects of cannabis.[13] CBD is not known to cause acute intoxication or euphoria and has low affinity for both CB1 and CB2 receptors but may modulate receptor signaling indirectly and interact with other receptors such as serotonin receptors and the TRPV1 ion channel, involved in pain perception and inflammation (**Figure 1**).[13,15]

Figure 1. Pharmacology of Cannabis Compounds



Regulatory Status

Most US states have legalized medical cannabis and many have legalized recreational use (the National Conference of State Legislatures maintains a current list of state medical cannabis laws, **Figure 2**).[16]

Regulatory bodies such as the US Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency establish rigorous requirements from clinical trials, adherence to Good Manufacturing Process guidelines, and quality standards on concentrations and other ingredients (eTable 1 in Supplement).

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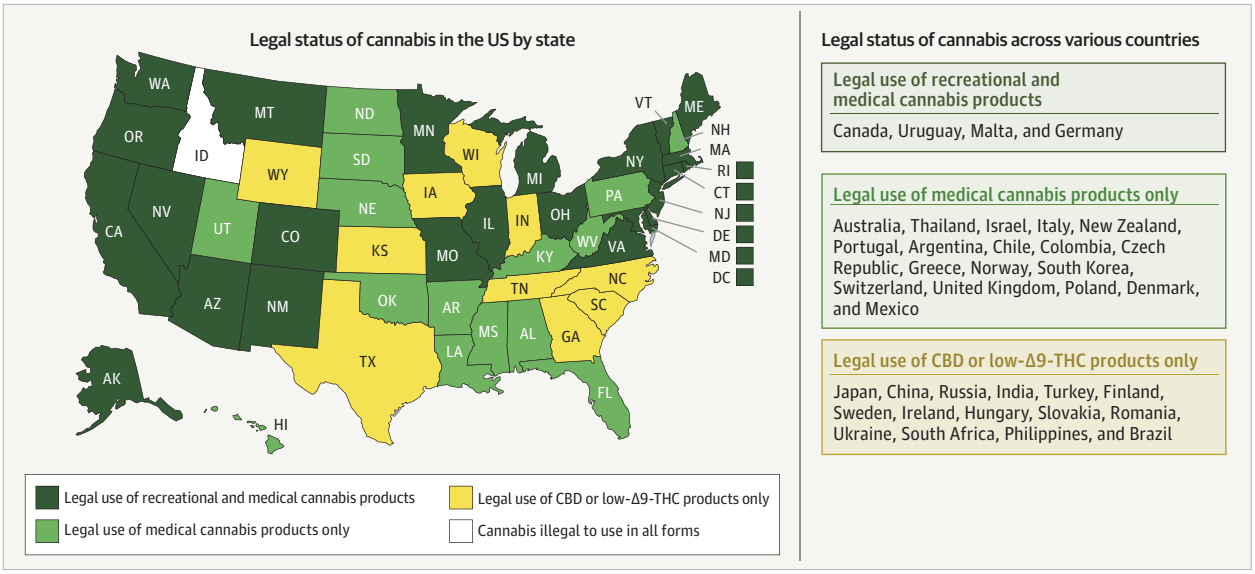
Figure 2. Cannabis Regulations in the US and Internationally as of August 1, 2025



In the US, pharmaceutical-grade cannabinoids (defined in Table 1) are classified as controlled substances under federal law and require a Drug Enforcement Administration (DEA) license to prescribe, with the exception of pharmaceutical-grade CBD, which was descheduled in 2020 (**Table 2**). Nabiximols (oral-mucosal spray containing Δ9-THC and CBD) is not currently FDA-approved in the US, although it is available in other countries such as Canada and the UK. In the US, over-the-counter cannabis products (eg, CBD oils, edibles) must contain less than 0.3% Δ9-THC.[23] These products are not FDA-approved, and compliance is enforced primarily at the state level, with variable testing and oversight.

Product Types

In 2023, the International Cannabis Policy Study surveyed a nationally representative sample of US adults[24] Among 64 054 participants (21.9% of the total sample) who used cannabis in the past year, 70% reported using dried flower, 59% edibles, 42% vape oils, 25% concentrates, 23% oral oils, 20% hash, 18% topicals, and 16% cannabis-infused drinks. Vaping involves heating cannabis oil or flower to a temperature that aerosolizes cannabinoids and other compounds without burning plant material. Smoking and vaping are popular methods of cannabis consumption due in part to their rapid onset of action, with blood Δ9-THC levels typically peaking within 30 minutes of inhalation.[25]

Cannabis can also be consumed orally via edibles (eg, gummies, brownies), tinctures (alcohol- or glycerin-based extracts), or capsules. The bioavailability of Δ9-THC is substantially lower when orally ingested (4%-12%) compared with inhaled (10%-35%).[26] Ingestion requires cannabinoids to pass through the digestive system, which delays the onset of action. The effects of cannabis edibles may not peak until 1 to 3 hours after consumption, with durations of action ranging from 1.5 to 12 hours depending on the dose.[27,28] Due to this delayed onset and limited awareness that a dose of 5 to 10 mg of Δ9-THC may comprise only a fraction of an edible (eg, brownies can contain 50-100 mg of Δ9-THC), individuals may inadvertently consume more Δ9-THC than intended. A retrospective study[29] of 9973 emergency department visits between 2012 and 2016 in Colorado reported that compared with those who inhaled cannabis, people who took edible cannabis had a higher frequency of psychiatric symptoms such as anxiety or acute psychosis (18.0% vs 10.9%; risk difference [RD], 7.1 percentage points [95% CI, 2.1-12.1]), intoxication (48% vs 28%; RD, 20.5 percentage points [95% CI, 13.9-27.1]), and cardiovascular symptoms such as tachycardia and hypertension (8.0% vs 3.1%; RD, 4.9 percentage points [95% CI, 1.4-8.4]).

Epidermal cannabis formulations include topical creams, balms, and patches, which do not produce psychoactive effects because they do not result in significant systemic absorption.[30]

The RCTs that form the basis for regulatory approval required the use of pharmaceutical-grade cannabinoids; the effectiveness and safety of nonpharmaceutical products and delivery methods such as vaping, gummies, and brownies have not been established in trials of similar rigor.

Medical Indications for Cannabis

Pharmaceutical-grade cannabinoids are FDA-approved for HIV/AIDS-induced anorexia, chemotherapy-induced nausea and vomiting, and several pediatric seizure disorders (Table 1 and Table 2). Use of FDA-approved cannabinoids for nonapproved conditions is considered off-label use, whereas use of non-FDA–approved cannabis or cannabinoids for medical purposes is considered over-the-counter use. Determining appropriate usage of cannabis or cannabinoids for non-FDA approved indications is challenging because qualifying conditions defined by laws and regulations are often not evidence-based. To minimize risk, screening to identify high-risk conditions (eg, cardiovascular disease or psychotic disorders) and potential drug-drug interactions (eg, CBD with warfarin or tacrolimus), is essential before considering prescribing cannabis or cannabinoids (**Table 3**).[43-47] We describe evidence for treatment of several medical conditions selected based on the availability of evidence and prevalence of cannabis or cannabinoid use reported for those conditions.[48]

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Table 2. Pharmaceutical-Grade Cannabinoids, Approved Conditions, and Adverse Effects

Cannabinoid	DEA schedule	FDA-approved indication	Route and dosing	Improvement vs placebo, SMD (95% CI)[a]	Common adverse effects[b]
CBD oral solution	No schedule	Dravet syndrome, Lennox-Gastaut syndrome, seizures associated with tuberous sclerosis	2.5 mg/kg 2/d (daily total maximum 20 mg/kg), orally	Reduction in seizure frequency, −0.50 (−0.62 to −0.38)[17,c]	Gastrointestinal symptoms: diarrhea, 59.5% vs 30.6% in placebo and active control groups; increased ALT and AST, 12.8% vs 0.3%; increased AST and/or ALT ≥3 times the normal limit, 6.4% vs 0%[18] Rash (6.4% vs 0.7%)[18] To monitor for potential hepatic injury, obtain serum transaminases (ALT, AST) and total bilirubin levels at baseline, at 1, 3, and 6 mo after initiation[18]
Dronabinol (synthetic THC)	Schedule II (oral solution) or Schedule III (capsule)	HIV/AIDS-induced anorexia	2.5 mg 2/d, orally	Improvement in appetite, −0.51 (−0.87 to −0.15)[17,d]	Dose-related high (elation, heightened awareness) in 24% of patients at antiemetic doses (5 mg every 2-4 h) vs 8% at appetite-stimulant doses (2.5 mg 2/d) Adverse reactions ≥3% incidence include abdominal pain, nausea, vomiting, dizziness, somnolence, and paranoia[19]
		Chemotherapy-induced nausea and vomiting	5 mg 1-3 h prior to chemotherapy, followed by 5 mg every 2-4 h thereafter (total of 4-6 doses daily), orally	Reduction in nausea and vomiting, −0.21 (−0.49 to 0.07)[17,d,e]	
Nabilone (CB1 receptor agonist)	Schedule II	Chemotherapy-induced nausea and vomiting	1-2 mg 2/d (daily total maximum 6 mg), orally	Reduction in nausea and vomiting, −0.23 (−0.55 to −0.08)[17,d,e]	Vertigo (52% vs 3% in placebo group) Drowsiness (52% vs 5%) Dry mouth (36% vs 2%) Ataxia (14% vs 0%) Euphoria (11% vs 1%) Sleep disturbance (11% vs 1%) Dysphoria (12% vs 0%) Headache (8% vs 0%)[20]
Nabiximols (oromucosal spray composed of approximately 1:1 Δ9-THC and CBD)	No schedule	Multiple sclerosis-related spasticity (not FDA-approved, but approved in several other countries [eg, UK, Spain, Germany])	Initiate with 1/d spray, increasing by 1 spray each day until reaching optimal relief or onset of adverse effects, typically over 1-2 wk	Reduction in spasticity symptoms, −1.41 (−1.65 to −1.17)[21,d]	Dizziness (31.7% vs 10% in placebo) Nausea (31.7% vs 10%) Fatigue (25.1% vs 18.8%) Dizziness and fatigue may impair functional capacity, particularly at initiation or dose escalation[22]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CB1, cannabinoid receptor type 1; CBD, cannabidiol; DEA, Drug Enforcement Administration; FDA, US Food and Drug Administration; SMD, standardized mean difference; THC, tetrahydrocannabinol.

[a] SMDs of 0.2, 0.5, and 0.8 are usually considered small, medium, and large, respectively.

[b] Reported by more than 3% of clinical trial participants. Adverse reactions listed are generally considered mild to moderate and self-limiting unless otherwise specified.

[c] Change in seizure frequency typically measured by percent reduction in seizures from baseline.

[d] Outcome measured using 1 to 10 numerical rating scale.

[e] Meta-analyses may include some participants with other etiologies for nausea and vomiting (eg, after surgical procedures).

FDA-Approved Indications for Cannabinoids

Chemotherapy-Induced Nausea and Vomiting

In 1985, the FDA approved dronabinol and nabilone for chemotherapy-induced nausea and vomiting. The 2024 American Society of Clinical Oncology (ASCO) guideline[49] recommends that for adults with cancer receiving moderately or highly emetogenic antineoplastic agents (eg, carboplatin, oxaliplatin) who experience nausea and vomiting refractory to first-line and second-line treatment (eg, olanzapine, dexamethasone), clinicians may consider prescribing dronabinol or nabilone (moderate-quality evidence) or a quality-controlled oral 1:1 Δ9-THC to CBD extract (eg, nabiximols or similar products manufactured under regulatory oversight to ensure consistent cannabinoid content and purity; low-quality evidence). The overall strength of this conditional recommendation was weak.

A meta-analysis[17] of 34 RCTs involving 2426 adult participants reported that prescribed cannabinoids (eg, dronabinol, nabilone) had a small but statistically significant effect on improving nausea and vomiting from various causes (eg, chemotherapy, cancer) compared with placebo or active comparators (eg, alizapride, chlorpromazine; SMD, −0.29 [95% CI, −0.39 to −0.18]). However, a 2025 systematic review and meta-analysis[50] reported no difference in chemotherapy-induced nausea and vomiting control between cannabinoids and antiemetics such as alizapride or chlorpromazine. The authors noted that most RCTs examining the effects of cannabinoids on chemotherapy-induced nausea and vomiting predated current triple or quadruple-agent prophylaxis and further studies are needed to evaluate the safety and efficacy of cannabinoids compared with modern regimens containing olanzapine.

Appetite Stimulation in HIV/AIDS

Dronabinol is FDA approved for treatment of HIV/AIDs-induced anorexia and may be considered for patients with persistent weight

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Table 3. Screening and Clinical Precautions Before Initiating Cannabis or Cannabinoids

Assessment	Recommendations
Underlying conditions and appropriateness of indication	Evaluate and address the underlying conditions contributing to the target symptom (eg, insomnia, pain, anxiety)
Informed consent	Discuss and document the risks, benefits, and alternatives of relevant cannabis or cannabinoid treatments
Conditions associated with increased risk	
Substance use disorder (SUD)	The American Society of Addiction Medicine recommends counseling patients of the potential harms of products containing Δ9-THC likely to exceed potential benefits because SUDs are a risk factor for cannabis use disorder[31,32]
	The College of Family Physicians of Canada suggests incorporating a structured assessment of substance use risk (eg, CAGE-AID questionnaire) prior to initiating cannabis treatment, especially for patients with a history of a SUD[33]
	Consider obtaining an initial urine drug screen,[54] checking the prescription drug monitoring program (a state-run electronic database) and obtaining informed consent for future urine drug screening. Currently no universally accepted clinical guidelines exist on the optimal frequency of urine drug screening for patients with SUDs considering cannabis or cannabinoids. Monitoring should be based on clinical judgment, SUD risk stratification, and treatment goals[33]
	Consider referral to addiction specialist
Mental illness	The American Psychiatric Association and American Society of Addiction Medicine recommend advising patients that the risks likely outweigh benefits regarding the use of therapeutics that contain Δ9-THC[31,34]
	Consider consultation with psychiatrist
Pulmonary disease	Recommend against the use of inhaled cannabis products, especially patients with pulmonary disease such as asthma or chronic obstructive pulmonary disease[31,35]
Cardiovascular disease (CVD)	Recommend counseling patients that the potential harms of therapeutics containing Δ9-THC likely outweigh the benefits among patients with moderate to severe CVD including ischemic heart disease, poorly controlled hypertension, severe heart failure, coronary artery disease, and arrhythmia[35-37]
	Recommend against inhaled cannabis products, including smoked and vape products, for patients with a history of CVD[35-37]
	Nabiximols are contraindicated for patients with serious CVD including poorly controlled hypertension and severe heart failure[37]
	Electrocardiogram prior to cannabis use is currently not supported by evidence
Fall risk or frailty	Recommend counseling patients with fall risk or frailty that potential harms of cannabis or cannabinoid use likely exceed potential benefits because cannabis and cannabinoids carry a risk of falls and CNS depression[31]
Severe liver disease	Recommend against the use of therapeutics containing Δ9-THC for patients with severe liver disease due to increased risk of fibrosis and steatorrhea[35,38]
Pregnancy, planning pregnancy, or breastfeeding	The American College of Obstetricians and Gynecologists and the American College of Physicians recommend that clinicians advise against the use of cannabis or cannabinoids among patients who are pregnant, are planning to become pregnant, or are breastfeeding (Table 3)[31]
Children, adolescents, and young adults (age ≤25 y)	Recommend against the use of cannabis during neurodevelopment (≤25 y), given evidence of potential long-term cognitive and psychiatric risks associated with early exposure to Δ9-THC, which likely outweigh therapeutic benefits[39,40]
Older adults (age ≥65)	Recommend caution when considering cannabis or cannabinoids due to age-related physiological changes including reduced hepatic function, risk of polypharmacy, CNS sensitivity, and reduced fat-free body mass, which may lead to increased adverse effects, particularly with therapeutics containing Δ9-THC[41]
	The Canadian Centre on Substance Use and Addiction recommends starting with no more than 1 to 2 puffs or doses daily of a product containing ≤10% THC with equal or higher CBD, or ≤2.5-mg THC with equal or higher CBD per edible[42]
	The Canadian Coalition for Seniors' Mental Health advises that clinicians screen for cognitive impairment, fall risk, and use of CNS depressants before initiating cannabis in adults aged ≥65 y[41]
Preexisting cannabis or cannabinoid use	Recommendations if a patient reports preexisting use of cannabis or cannabinoids for medical reasons:
	Assess for frequency, duration, product type, potency, delivery mechanism, mode of procurement (eg, dispensary, unregulated markets)
	Discuss risks, benefits, and FDA-approved or evidence-based alternatives for current cannabis and/or cannabinoid use
	If risks of preexisting cannabis use likely outweigh benefits, recommend a gradual taper rather than abrupt discontinuation in patients with long-term, heavy cannabis use to reduce the risk of withdrawal syndrome35
	Review harm reduction strategies including avoidance of high-potency use (containing >10% [inhaled] or >10 mg/d [oral] Δ9-THC; Table 4)
	If use is chronic (>1 y), frequent (>1wk), or high potency:
	Assess for acute intoxication, cannabis use disorder, and cannabis withdrawal syndrome using criteria from the *DSM-5*
	Assess for cannabis hyperemesis syndrome

(continued)

loss despite antiretroviral therapy, although supporting evidence is limited and of low quality.[51-53] A 2018 meta-analysis[54] of 192 adult participants with HIV in 2 RCTs reported that cannabinoids (2.5-mg dronabinol capsule or 3.95% Δ9-THC cannabis cigarette) had a moderate effect on increasing body weight (SMD, 0.57 [95% CI, 0.22 to 0.92]), although the quality of evidence was very low.

Seizures

The FDA approved pharmaceutical-grade CBD as adjunctive therapy for seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients 2 years or older and for tuberous sclerosis complex in patients aged 1 year or older. The American Academy of Neurology and American Epilepsy Society support the use of FDA-approved CBD in combination with other antiepileptic medications for these childhood seizure disorders.[55] A meta-analysis[17] (6 double-blind RCTs with 948 pediatric patients with treatment-resistant childhood-onset epilepsy and 8 healthy adult volunteers) reported that CBD compared with placebo had a moderate effect on reducing seizure frequency (SMD, −0.50 [95% CI, −0.62 to −0.38]). Evidence remains insufficient to recommend cannabis or cannabinoids for treatment of epilepsy in adults (eTable 2 in the Supplement).[55-57]

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Table 3. Screening and Clinical Precautions Before Initiating Cannabis or Cannabinoids (continued)

Assessment	Recommendations
Drug-drug interactions	Review patient's medication list for clinically significant drug-drug interactions when considering cannabis or cannabinoid therapy
	Avoid or use caution when combining cannabis or cannabinoids with other sedating medications (eg, benzodiazepines, opioids, sedating antidepressants) due to additive and/or synergistic CNS depressant effects[43]
	Clinically relevant drug-drug interactions:
	Cannabis smoking can induce the CYP1A2 enzyme, potentially lowering concentrations of certain medications (eg, olanzapine and clozapine)
	Strong CYP3A4 inhibitors (eg, ketoconazole) can increase Δ9-THC and CBD levels, increasing sedation and potential psychoactive effects[44]
	CYP3A4 inducers (eg, rifampicin) can reduce concentrations of Δ9-THC and CBD[44,45]
	Δ9-THC containing products:
	Δ9-THC is a weak inhibitor of CYP3A4 and CYP2C9; however, at higher doses or in the presence of other CYP inhibitors, clinically relevant interactions may occur, potentially increasing levels of medications such as warfarin (monitor INR) and immunosuppressants (eg, tacrolimus, cyclosporine)[46]
	CBD-containing products:
	Due to CBD inhibition of CYP2C19 (strong), CYP3A4 (moderate), and CYP2D6 (weak to moderate), anticipate increased serum levels of medications such as certain selective serotonin reuptake inhibitors (eg, citalopram), warfarin (monitor INR), antiepileptics (eg, clobazam, esclicarbazepine, brivaracetam), and immunosuppressants (eg, tacrolimus, cyclosporine)[45,46]
	Coadministration of CBD with stiripentol or valproate may increase the risk of hepatotoxicity[45]

Abbreviations: CNS, central nervous system; CYP1A2, polymorphic cytochrome P450 1A2; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); INR, international normalized ratio; THC, tetrahydrocannabinol.

Conditions Not Approved by FDA

Chronic Noncancer Pain

The International Association for the Study of Pain, the American College of Physicians (ACP), and the Canadian Rheumatology Association (CRA) recommend against use of cannabis or cannabinoids as first-line treatment for chronic noncancer pain due to limited evidence of benefit and well-documented risks.[31,49,58] The ACP's[59] 2025 best practice advice suggests that nabiximols may be considered for patients whose neuropathic pain does not improve with first-line therapies (eg, tricyclic antidepressants, topical agents), based on moderate-certainty evidence. A meta-analysis[31] of 4 RCTs and 733 adult participants with chronic pain (eg, neuropathic pain, osteoarthritis, fibromyalgia) reported that nabiximols improved pain severity compared with placebo (MD, −0.54 [95% CI, −0.95 to −0.19]).

Low-certainty evidence suggests that purified Δ9-THC preparations with a high Δ9-THC to CBD ratio (eg, dronabinol, nabilone) may reduce chronic noncancer pain severity although without clear effect on function or disability.[31] A meta-analysis[59] of 8 RCTs (n = 684 patients) reported a large effect on improvement in chronic, noncancer pain severity with high Δ9-THC to CBD ratio preparations compared with placebo (SMD, −1.25 [95% CI, −2.09 to −0.71]). However, due to the heterogeneity of formulations, dosing strategies, and study designs, further high-quality research is needed before these preparations can be recommended.

The ACP and CRA recommend against use of inhaled cannabis to treat chronic noncancer pain because the risk of adverse effects such as chronic bronchitis and exposure to contaminants likely outweigh the benefits.[31,36]

Spasticity Due to Multiple Sclerosis

The American Academy of Physical Medicine and Rehabilitation 2024 consensus guidance[60] suggests further study before recommending cannabis or cannabinoids for multiple sclerosis (MS)–related spasticity. Although currently not FDA-approved in the US, nabiximols is approved in several other countries including Canada, the UK, France, and Germany for MS-related spasticity unresponsive to first-line treatments. The UK's National Institute for Health and Care Excellence recommends offering a 4-week trial of nabiximols for moderate-to-severe MS-related spasticity in adults who have not responded adequately to other antispasticity medications, with continuation only if associated with a clinically meaningful improvement (≥20% reduction on a 1-10 numeric rating scale).[61] A 2024 systematic review and meta-analysis[21] of 8780 adults with MS-related spasticity across 31 studies (both randomized and nonrandomized) reported that nabiximols had a large effect on improving spasticity symptoms on the numeric rating scale (SMD, −1.41 [95% CI, −1.65 to −1.17]).

There is currently insufficient evidence to recommend for or against formulations aside from nabiximols for the treatment of spasticity in MS.[62,63]

Cancer Pain

The 2024 ASCO guidelines[49] state that there is currently insufficient evidence to recommend for or against use of cannabis or cannabinoids to treat cancer pain. A meta-analysis[64] of 4 RCTs that included 1333 adults with opioid refractory cancer pain reported moderate-certainty evidence that there was no clinical benefit with nabiximols, for proportions of patient global impression of change (a patient-reported measure rating overall change in condition) much or very much improved compared with placebo (320 per 1000 vs 230 per 1000; risk difference, 0.06 [95% CI, 0.01-0.12]).

Insomnia

The 2022 World Sleep Society[65] and Kaiser Permanente Insomnia guidelines[66] do not recommend use of cannabis or cannabinoids for treatment of insomnia; the World Sleep Society cited insufficient supporting evidence and issued a weak recommendation against its use based on low-quality data.

A meta-analysis of 39 RCTs,[67] 38 of which evaluated oral cannabinoids and 1 administered inhaled cannabis, that included 5100

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adult participants with chronic pain reported that cannabis and cannabinoid use, compared with placebo, resulted in a small improvement in sleep quality (modeled risk difference [RD] for achieving the minimal clinically important difference, 8% [95% CI, 3%-12%]; moderate-certainty evidence) and sleep disturbance (modeled RD, 19% [95% CI, 11%-28%]; moderate- to high-certainty evidence). However, limitations of the meta-analysis included limited use of validated sleep measures and insufficient data on dose-response relationships, long-term outcomes, and concurrent medication use.

Dementia

RCT evidence suggests that cannabis or cannabinoids have no effect on prevention or treatment of dementia, and there is currently insufficient evidence to recommend for or against the use of cannabis or cannabinoids to treat behavioral or psychological symptoms of dementia such as aggression. A systematic review and meta-analysis[68] of 4 RCTs and 126 adult participants with dementia (106 with Alzheimer disease; 8, vascular dementia; 12, mixed Alzheimer disease or vascular dementia) reported that synthetic Δ9-THC analogues (eg, nabilone, dronabinol) compared with placebo had little or no clinically important effect on cognition as measured by the Mini-Mental State Examination (mean difference [MD], 1.1 points [95% CI, 0.1 to 2.1]; the minimal clinically important difference [MCID] on the Mini-Mental State Examination for dementia is 1.4). The meta-analysis also reported low-certainty evidence that there is little to no clinically important effect of cannabinoids on behavioral or psychological symptoms of dementia (measured by the Neuropsychiatric Inventory Questionnaire; MD, −1.97 [95% CI, −3.81 to −0.07]; 1 parallel group and 2 crossover studies, 110 participants; MCID is 8).

Psychiatric Indications

The American Psychiatric Association and American Society of Addiction Medicine recommend against use of cannabis or cannabinoids to treat any psychiatric disorder and emphasize that cannabis may exacerbate or precipitate mental illness, particularly psychosis and suicidality in individuals with depression.[33,34,69-75]

The 2023 Veterans Affairs and Department of Defense Clinical Practice Guideline[76] strongly recommend against use of cannabis or cannabinoids for the treatment of posttraumatic stress disorder (PTSD) due to low-quality evidence and known psychiatric adverse effects. A double-blind, randomized crossover trial[77] of 80 US veterans with PTSD reported no significant between-group difference in the Clinician-Administered PTSD Scale among participants given a medicinal inhaled cannabis with a combination of 0.5% to 12% Δ9-THC and less than 0.01% to 11% CBD content and those receiving placebo (P = .15).

Although current evidence is insufficient to recommend for or against CBD to treat anxiety disorders, preliminary support for its potential efficacy has emerged from small RCTs including less than 100 participants.[78] CBD may counteract the psychoactive and anxiogenic effects of Δ9-THC through indirect blockade of the CB1 receptor and upregulation of the anxiolytic endocannabinoid anandamide.[79] A 2024 systematic review and meta-analysis[78] of 316 adult patients in 8 studies (randomized and nonrandomized) reported that oral CBD had a large effect on reducing anxiety symptoms in patients with anxiety disorders (eg, generalized anxiety disorder, social anxiety disorder) compared with placebo (Hedges g = −0.92 [95% CI, −1.80 to −0.04]). However, limitations such as small sample sizes, brief trial durations (110 minutes to 12 weeks), and heterogeneity in target indications defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*; eg, generalized anxiety disorder, obsessive compulsive disorder) and CBD formulations limit clinical applicability of this study.

There is currently insufficient evidence regarding the use of cannabis or cannabinoids for many other medical conditions including acute pain,[80-82] Parkinson disease,[83] glaucoma,[84,85] and rheumatic diseases (eTable 2 in the Supplement).[86-88]

Risks, Harms, and Clinical Guidance to Minimize Harm

Clinicians should screen patients for conditions such as pregnancy and schizophrenia, in which potential harms of cannabis or cannabinoid use likely outweigh the benefits (Table 3).[89] Clinicians should also consider the clinical context when evaluating the potential therapeutic use of cannabis or cannabinoids because the balance of risks and benefits may differ substantially across patient populations and scenarios and should guide decision-making accordingly. For example, clinicians may be more willing to accept a less favorable risk-benefit profile when prescribing cannabinoids for a patient with advanced cancer than for a young healthy patient.

Cannabinoids

Common adverse effects of pharmaceutical-grade cannabinoids reported in RCTs are summarized in Table 2. Patients prescribed therapeutics containing Δ9-THC such as dronabinol and nabilone should be advised not to operate motor vehicles or heavy machinery for at least 6 to 8 hours after inhaled or oral pharmaceutical-grade cannabinoid use or 8 to 12 hours after edible (eg, brownies) use because blood Δ9-THC concentration of 2 to 5 ng/mL is associated with significant driving impairment.[19,20,22,90,91] The FDA also cautions that concurrent use of cannabinoids with central nervous system depressants (eg, benzodiazepines, alcohol) may increase sedation, dizziness, and somnolence.[19,37,38] In trials of pharmaceutical-grade CBD for tuberous sclerosis complex, somnolence occurred more frequently in pediatric and adult participants receiving concomitant clobazam compared with those not taking clobazam (33% vs 14%).[18] Prospective studies with longer duration of follow-up are needed to improve understanding of the chronic effects of cannabinoid use.

Cannabis

Patients may present with preexisting self-directed use of cannabis for medical purposes, such as products obtained from dispensaries or unregulated markets (Table 1), which tend to have higher potency and greater risks than FDA-approved formulations.[1-4,92] An observational study[1] of 8505 cannabis products from 653 US dispensaries reported that the average Δ9-THC content of cannabis labeled as medicinal (19.2% Δ9-THC content [95% CI, 18.97%-19.63%]) was comparable with products labeled as recreational (21.5% [95% CI, 21.37%-21.63%]), and on average exceeded Δ9-THC content used in clinical trials for treatment of conditions such as neuropathic pain (typically <10% Δ9-THC).[93] The distinction between medical and recreational cannabis reflects dispensary labeling practices and patient reason for use more than differences in potency and chemical composition.

Cannabis use may lead to acute intoxication, which may cause impaired motor coordination, euphoria, anxiety, sensation of slowed

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Table 4. Potential Adverse Effects of Cannabis Use

Category	Description	Evidence[a,b]
Overall effects		
Neurocognitive effects	Acute impairment in judgment and motor coordination	Increased risk of MVC fatality of 14 deaths per 100 000 MVCs[91]
	Chronic impairment in memory, attention, executive function, learning, processing speed	Small to moderate deficits in learning, speed of information processing, delayed memory, executive functioning or working memory, attention, cognitive flexibility, and impulsivity[95,96]
		Neurocognitive deficits from cannabis use in adults may be reversible after approximately 25 d of abstinence[97]
Psychiatric effects	Acute psychotic symptoms, particularly with high potency products	With high-potency (≥10% THC) vs lower-potency (<10% THC) cannabis use, association with psychotic-like experience (12.4% vs 7.1%), generalized anxiety disorder (19.1% vs 11.6%)[3]
	Chronic increased risk of developing psychotic disorders, anxiety, depression, and dependency	Increased risk of precipitating and/or worsening psychiatric disorders such as bipolar disorder,[71] schizophrenia,[72,73] and major depressive disorder[74]
		Increased suicidal ideation among patients with underlying depression, association with cannabis use in a dose-dependent manner[75]
Cardiovascular effects	Acute tachycardia, orthostatic hypotension, increased risk of MI and stroke in at-risk populations	When comparing daily inhaled cannabis use with nondaily use, increased risk of coronary heart disease (2.0% vs 0.9%), MI (1.7% vs 1.3%), and stroke (2.6% vs 1.0%), after adjusting for tobacco use[98]
	Increased risk of coronary artery disease, MI, and stroke with chronic and/or heavy use	
Respiratory effects (inhaled cannabis formulations)	Acute bronchial irritation, increased phlegm production, acute bronchitis	Among individuals vaping cannabis 3 or more days in the past 30 d compared with no lifetime history of cannabis use, increased frequency of bronchitis symptoms (23.2% vs 12.3%) and wheezing (20% vs 10.3%)[99]
	Chronic bronchitis, cough, wheezing, phlegm production, asthma	
Pregnancy and breastfeeding	Δ9-THC and CBD cross the placenta and concentrate in breast milk due to their lipophilicity, exposing the fetus and infant to cannabinoids	Cannabis use during pregnancy compared vs no use is associated with low birth rate (11.9% vs 7.1%), small for gestational age (14.3% vs 8.4%), decreased mean neonatal head circumference (mean difference, −0.52 cm), and increased neonatal ICU admissions (10% vs 6.7%)[89]
Cannabis-induced syndromes		
Cannabis hyperemesis syndrome	Recurrent episodes of intractable nausea, vomiting, and abdominal pain in individuals with chronic heavy cannabis use, typically relieved by hot bathing or cessation of cannabis	Prevalence 32.9% among patients who smoked cannabis ≥20 d/mo[100]
		To address the acute symptoms, the American Gastroenterology Association[101] recommends counseling on cannabis cessation
		Short-term management may include topical capsaicin, benzodiazepines, olanzapine, and haloperidol
		Long-term management may include tricyclic antidepressants such as amitriptyline (75-100 mg at bedtime)
Cannabis withdrawal syndrome	Per the *DSM-5*,[94] cannabis withdrawal syndrome is diagnosed when ≥3 symptoms (eg, irritability, anxiety, or sleep disturbances) develop within approximately 1 wk after cessation of heavy and prolonged cannabis use	Among patients who regularly use cannabis or have a diagnosis of cannabis use disorder, prevalence is 17% (95% CI, 13%-21%)[102]
		Typically managed with supportive care, including reassurance, sleep, and appetite stimulation (eg, nutritional counseling, high-calorie supplements), and, in more severe cases, short-term use of medications such as gabapentin[103]
Cannabis use disorder	Per the *DSM-5*,[94] cannabis use disorder is diagnosed by the presence of at ≥2 of 11 criteria—such as impaired control over use, social or occupational impairment, risky use, tolerance, or withdrawal—occurring within a 12-mo period and causing clinically significant impairment or distress	29% (95% CI, 21%-38%) of individuals who self-report medicinal cannabis use within the past 6-12 mo meet criteria for cannabis use disorder[104]

Abbreviations: CBD, cannabidiol; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); ICU, intensive care unit; MI, myocardial infarction; MVC, motor vehicle collision; THC, tetrahydrocannabinol.

[a] Chronic risks should be interpreted with caution because they are largely based on retrospective studies that cannot establish causality.

[b] See eTable 3 in the Supplement for detailed effect sizes and confidence intervals.

time, impaired judgment, social withdrawal, conjunctival injection, increased appetite, dry mouth, and tachycardia.[94] Serious acute adverse effects, such as psychosis and myocardial infarction, may occur in individuals with certain underlying conditions (eg, schizophrenia, cardiovascular disease) and/or with the use of high-potency cannabis products, including edibles, where delayed onset can lead to inadvertent overconsumption; these serious adverse effects are further described in **Table 4**.

Clinicians should evaluate patients using cannabis for potential cannabis use disorder, characterized by the presence of at least 2 out of 11 *DSM-5*[94] criteria (**Box 2**).[32,104] Additional long-term health effects of cannabis are uncertain because many commonly used products, particularly high-potency formulations, have not been studied in RCTs. Based on observational studies, clinicians should be aware of potential health risks associated with cannabis use, particularly when counseling patients with relevant medical conditions

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Box 2. Diagnosis of Cannabis Use Disorder

The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) indicates that a diagnosis of cannabis use disorder occurs when 2 of 11 of the following characteristics occur within a 12-month period.[94]

- Using more cannabis than originally intended
- Struggling to control or reduce cannabis use
- Spending considerable time obtaining, using, or recovering from cannabis
- Experiencing cravings for cannabis
- Facing problems at work, school, or home due to cannabis use
- Continuing cannabis use despite social or relationship issues caused by it
- Abandoning or reducing important activities in favor of cannabis use
- Using cannabis in situations that are physically hazardous
- Persisting in cannabis use despite awareness of physical or psychological problems
- Developing tolerance to cannabis, requiring more to achieve the same effect
- Experiencing withdrawal symptoms when not using cannabis

(eg, underlying psychiatric or cardiac conditions) or using high-potency cannabis products (Table 3). Clinicians should also be familiar with the presentation and recommended treatment of cannabis-induced syndromes such as cannabis hyperemesis syndrome and cannabis withdrawal syndrome (Table 4).[38,39,41,42,100-103]

Cardiovascular Risks

Evidence from observational studies and meta-analyses suggest an association between cannabis use and increased risk of acute cardiovascular events, including myocardial infarction, stroke, arrhythmias, and cardiovascular mortality (Table 4).[98,105,106] For example, a large multicenter study[106] of 4 636 628 relatively healthy (ie, no cardiovascular comorbidities such as hypertension, hyperlipidemia, coronary artery disease) adults aged 50 years or younger who did not use tobacco reported that cannabis use, defined by chart documentation of cannabis-use-related *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes, was associated with a higher absolute risk of myocardial infarction compared with nonuse (0.55% vs 0.09%; risk ratio, 6.18 [95% CI, 4.89-7.82]).

Proposed mechanisms underlying these cardiovascular effects include Δ9-THC–induced sympathetic nervous system activation, increased myocardial oxygen demand, coronary vasospasm, and impaired vascular reflexes.[35,107,108] Cannabis use may also contribute to endothelial dysfunction (ie, impaired endothelium-dependent vasodilation), an early marker of atherosclerosis that can increase long-term cardiovascular risk.[109] Therefore, clinicians should assess cardiovascular risk before prescribing cannabis for medical purposes, optimize treatment of conditions associated with cardiovascular disease (eg, hypertension, dyslipidemia, tobacco use), and counsel on use of lower-dose and potency formulations (**Table 5**). Clinicians should consider monitoring for symptoms such as palpitations, presyncope, or chest pain, especially within the first 1 to 2 hours after use when adverse effects are most likely to occur.

Pulmonary Risks

Clinicians should recommend against the use of inhaled cannabis, especially among patients with asthma or chronic obstructive pulmonary disease.[31,35] The American Thoracic Society offers a patient education resource outlining the potential harmful effects of cannabis use on lung health. Observational studies suggest that inhaled cannabis consumption may be associated with increased risk of asthma, chronic cough, dyspnea, wheezing, and increased sputum production (Table 4).[99,112,113]

Neurocognitive Risks

Observational studies and meta-analyses suggest that chronic cannabis use, defined as 12 or more months of continuous and recurrent cannabis consumption, may be associated with small to medium effect size deficits across several neurocognitive domains, including learning, processing speed, memory, executive functioning, and attention (Table 4).[95,96,114] However, in adults older than 25 years, observational studies and meta-analyses suggest that cannabis-induced neurocognitive deficits may attenuate after prolonged abstinence (25 days), once acute intoxication and withdrawal effects wear off.[95,97] Prospective research is needed to clarify the long-term neurocognitive risks of cannabis use, including risks of developing dementia.[114]

Contamination and Quality Control

Unlike pharmaceutical-grade cannabinoids, which are subject to FDA regulations on purity, potency, and contaminants, most products sold in dispensaries are not held to consistent national standards. Cannabis products sold at US dispensaries are regulated at the state level, leading to wide variability across the US in cannabis product quality, labeling accuracy, and testing standards.[110,115] This regulatory gap contributes to cannabis products' potential risk of contamination with mold, heavy metals, pesticides, and other potentially harmful toxins (**Table 6**).[116,117,119-121] The American Heart Association recommends that clinicians advise patients against obtaining cannabis or cannabinoid products through unregulated markets due to heightened risk of contamination, adulteration, and unpredictable potency.[35,118] There is insufficient evidence to determine whether growing cannabis plants is safer than using products sold at a dispensary.

Practical Considerations and Application of Evidence

Informed Consent and Shared Decision-Making

The informed consent process should include a discussion of risks and benefits associated with cannabis use along with FDA-approved alternatives. Clinicians should adopt a nonjudgmental approach and encourage an open dialogue with patients. Patients often underreport cannabis and cannabinoid use in clinical settings,[48] due to stigma, fear, and mistrust, which can impede effective communication with clinicians about medical use of cannabis and cannabinoids.[122] Clinicians who deem a patient appropriate for a trial of cannabis or cannabinoids may certify the patient for a medical cannabis card or refer them to another clinician who can certify the patient. This certification is not a prescription for medical cannabis, but rather a statement that the patient meets the qualifying criteria under state law. Clinicians should be familiar with institutional policies because some federally funded systems, such as the US Department of

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Table 5. Harm Reduction and Informed Use Strategies

Strategy	Details
Use lower Δ9-THC potency formulations when possible	Prefer products with <10% Δ9-THC (inhaled) or ≤5-mg Δ9-THC per serving (edible), particularly for individuals new to cannabis or with underlying medical conditions (eg, cardiovascular or respiratory conditions) or psychiatric conditions; use the lowest effective dose to minimize adverse effects[38,110]
Prefer noninhaled routes	Select oral or sublingual formulations over smoking or vaping to reduce risks to lung health
Start low, go slow	The Canadian Centre on Substance Use and Addiction recommends starting with no more than 1 to 2 puffs or doses daily of a product containing ≤10% THC with equal or higher CBD, or ≤2.5-mg THC with equal or higher CBD per edible[42]
Avoid combining cannabis with other substances	Do not use cannabis or cannabinoids with alcohol, opioids, or other central nervous system depressants due to increased risk of adverse effects such as respiratory depression and/or somnolence
Avoid driving or operating machinery after cannabis use	Counsel patients not to drive or operate machinery for at least 6-8 h after inhaling cannabis or taking pharmaceutical-grade oral cannabinoids and 8-12 h after edible use because blood Δ9-THC concentration of 2-5 ng/mL is associated with significant driving impairment[90]
Store products safely	Keep cannabis or cannabinoids in child-resistant containers, stored securely and out of reach of children, adolescents, and pets
Monitor for drug-drug interactions	Monitor for potential interactions between cannabis or cannabinoids and other prescription and over-the-counter medications, particularly those metabolized by cytochrome P450 enzymes (eg, CYP3A4, CYP2C9, CYP2C19)
Avoid cannabis products sold through unregulated markets	Cannabis from unregulated markets such as online marketplaces or unlicensed dispensaries may have higher risk of contamination, mislabeling, or adulteration with harmful substances, including synthetic cannabinoids, compared with products from licensed dispensaries or pharmaceutical-grade products[5]
Delay initiation of cannabis use until >25 y[40]	A recent systematic review[111] reported both transient (eg, mood) and potentially persistent neurocognitive effects (eg, cognitive function, sensory functioning) in youth and adolescents, underscoring the need for caution when considering cannabis or cannabinoid use in youth

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol.

Table 6. Potential Contaminants in Cannabis or Cannabinoids Used for Therapeutic Purposes

Contaminant	Clinical concern	Evidence
Pesticides	Respiratory irritation, neurotoxicity, cardiotoxicity	In a Canadian observational study[116] of cannabis inflorescence (flowering tops of the plant that are typically harvested and consumed), 22 of 24 (92%) of unregulated market samples tested positive for pesticides; 2 of 36 (6%) of licensed (regulated) products contained detectable pesticide residues
Heavy metals	Neurotoxicity, nephrotoxicity, and cardiotoxicity with chronic exposure	An observational study[117] of 97 edible CBD products purchased from US dispensaries and unregulated markets reported detectable lead in 70% of samples, with 4% (4 of 97) exceeding the California Proposition 65 daily threshold for lead exposure
Fungi	Pulmonary aspergillosis and other invasive fungal infections, particularly among immunocompromised individuals	A retrospective study[5] of US commercial claims data (n = 21 612 775) reported higher rates of fungal infections among patients with than those without a cannabis use-related *ICD-10* diagnostic code (0.08% vs 0.03%; OR, 2.6 [95% CI, 1.9 -3.5]). *Aspergillus* species were the most common fungal infection reported in this study
Fentanyl	Risk of unintentional opioid exposure and overdose	Rare case reports in the US have described cannabis adulterated with fentanyl, typically involving products from unregulated or illegal markets; however, such occurrences are exceedingly uncommon and do not warrant routine fentanyl testing or public health surveillance[118]

Abbreviations: CBD, cannabidiol; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*

Veterans Affairs, prohibit recommending cannabis for medical use (per Veterans Health Administration directive 1315; eTable 1 in the Supplement).

Use Agreements and Care Plans

Clinicians certifying cannabis for medical purposes for their patients may consider using a written informed consent or treatment agreement. Originally developed to reduce liability in the context of opioid prescribing,[123] treatment agreements can provide a structured framework for medical cannabis use. Key components may include guidance on safe storage, particularly keeping cannabis out of reach of children and adolescents; procedures to follow if a patient develops high-risk condition (eg, pregnancy); discussion of potential adverse effects such as impaired driving and interactions with opioids, benzodiazepines, or alcohol; and expectations regarding follow-up visit intervals.[40,111,124] An example treatment agreement is available from the College of Family Physicians of Canada.

Limitations

This review has several limitations. First, this is not a systematic review, and we did not conduct a formal risk of bias assessment of included studies. Second, many of the studies included in this review were observational and may be subject to confounding. Third, recommendations based on RCTs may not directly apply to individual patients, given heterogeneity of study designs, patient populations, cannabis formulations, and dosing. Fourth, some relevant articles may have been missed.

Conclusions

Evidence is insufficient for the use of cannabis or cannabinoids for most medical indications. Clear guidance from clinicians is essential to support safe, evidence-based decision-making. Clinicians should weigh benefits against risks when engaging patients in informed discussions about cannabis or cannabinoid use.

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REFERENCES

1. 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

2. 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. doi:10.1016/S2215-0366(22)00161-4

3. Hines LA, Freeman TP, Gage SH, et al. Association of high-potency cannabis use with mental health and substance use in adolescence. *JAMA Psychiatry*. 2020;77(10):1044-1051. doi:10.1001/jamapsychiatry.2020.1035

4. 7 Things you need to know about edible cannabis. Canadian Centre on Substance Use and Addiction; 2019. Accessed June 30, 2025. https://www.ccsa.ca/sites/default/files/2019-06/CCSA-7-Things-About-Edible-Cannabis-2019-en.pdf

5. Tagen M, Klumpers LE. Review of delta-8-tetrahydrocannabinol (Δ^8-THC): comparative pharmacology with Δ^9-THC. *Br J Pharmacol*. 2022;179(15):3915-3933. doi:10.1111/bph.15865

6. Sepulveda DE, Morris DP, Raup-Konsavage WM, Sun D, Vrana KE, Graziane NM. Cannabigerol (CBG) attenuates mechanical hypersensitivity elicited by chemotherapy-induced peripheral neuropathy. *Eur J Pain*. 2022;26(9):1950-1966. doi:10.1002/ejp.2016

7. Leung J, Chan G, Stjepanović D, Chung JYC, Hall W, Hammond D. Prevalence and self-reported reasons of cannabis use for medical purposes in USA and Canada. *Psychopharmacology (Berl)*. 2022;239(5):1509-1519. doi:10.1007/s00213-021-06047-8

8. Park JY. Patterns of cannabidiol use among marijuana users in the United States. *Prev Med Rep*. 2025;50:102985. doi:10.1016/j.pmedr.2025.102985

9. Weisman JM, Rodríguez M. A systematic review of medical students' and professionals' attitudes and knowledge regarding medical cannabis. *J Cannabis Res*. 2021;3(1):47. doi:10.1186/s42238-021-00100-1

10. Makki I, Zheng-Lin B, Kohli M. Medical marijuana knowledge and attitudes amongst internal medicine residents. *BMC Prim Care*. 2022;23(1):38. doi:10.1186/s12875-022-01651-9

11. Rønne ST, Rosenbæk F, Pedersen LB, et al. Physicians' experiences, attitudes, and beliefs towards medical cannabis: a systematic literature review. *BMC Fam Pract*. 2021;22(1):212. doi:10.1186/s12875-021-01559-w

12. Hill KP. Medical use of cannabis in 2019. *JAMA*. 2019;322(10):974-975. doi:10.1001/jama.2019.11868

13. Kendall DA, Yudowski GA. Cannabinoid receptors in the central nervous system: their signaling and roles in disease. *Front Cell Neurosci*. 2017;10:294. doi:10.3389/fncel.2016.00294

14. Pacher P, Steffens S, Haskó G, Schindler TH, Kunos G. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol*. 2018;15(3):151-166. doi:10.1038/nrcardio.2017.130

15. Maresz K, Pryce G, Ponomarev ED, et al. Direct suppression of CNS autoimmune inflammation via the cannabinoid receptor CB1 on neurons and CB2 on autoreactive T cells. *Nat Med*. 2007;13(4):492-497. doi:10.1038/nm1561

16. Liu EY, McCall KL, Piper BJ. Pronounced state-level disparities in prescription of cannabinoids to Medicaid patients. *Med Cannabis Cannabinoids*. 2023;6(1):58-65. doi:10.1159/000531058

17. Bilbao A, Spanagel R. Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications. *BMC Med*. 2022;20(1):259. doi:10.1186/s12916-022-02459-1

18. Epidiolex (cannabidiol). Package insert. Jazz Pharmaceutical. 2018. Accessed August 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

19. Dronabinol. Package insert. AbbVie Accessed August 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018651s033lbl.pdf

20. US Food and Drug Administration (FDA). Nabilone. Package insert. Published online 2006. Accessed August 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf

21. Azadvari M, Pourshams M, Guitynavard F, et al. Cannabinoids for spasticity in patients with multiple sclerosis: a systematic review and meta-analysis. *Mult Scler J Exp Transl Clin*. 2024;10(4):20552173241282379. doi:10.1177/20552173241282379

22. Prieto González JM, Vila Silván C. Safety and tolerability of nabiximols oromucosal spray: a review of more than 15 years' accumulated evidence from clinical trials. *Expert Rev Neurother*. 2021;21(7):755-778. doi:10.1080/14737175.2021.1935879

23. Liebling JP, Clarkson NJ, Gibbs BW, Yates AS, O'Sullivan SE. An analysis of over-the-counter cannabidiol products in the United Kingdom. *Cannabis Cannabinoid Res*. 2022;7(2):207-213. doi:10.1089/can.2019.0078

24. Teutsch S, Hurd Y, Boyle E, eds. *Cannabis Policy Impacts Public Health and Health Equity*. National Academies Press; 2024. doi:10.17226/27766

25. Spindle TR, Cone EJ, Schlienz NJ, et al. Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis: a crossover trial. *JAMA Netw Open*. 2018;1(7):e184841. doi:10.1001/jamanetworkopen.2018.4841

26. Chayasirisobhon S. Mechanisms of action and pharmacokinetics of cannabis. *Perm J*. 2020;25:1-3.

27. Schlienz NJ, Spindle TR, Cone EJ, et al. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. *Drug Alcohol Depend*. 2020;211:107969. doi:10.1016/j.drugalcdep.2020.107969

28. Vandrey R, Herrmann ES, Mitchell JM, et al. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. *J Anal Toxicol*. 2017;41(2):83-99. doi:10.1093/jat/bkx012

29. Monte AA, Shelton SK, Mills E, et al. Acute illness associated with cannabis use, by route of exposure: an observational study. *Ann Intern Med*. 2019;170(8):531-537. doi:10.7326/M18-2809

30. 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

31. Kansagara D, Hill KP, Yost J, et al; Population Health and Medical Science Committee of the American College of Physicians. 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

32. Hasin DS, Kerridge BT, Saha TD, et al. Prevalence and correlates of *DSM-5* cannabis use disorder, 2012-2013: findings from the national epidemiologic survey on alcohol and related conditions-III. *Am J Psychiatry*. 2016;173(6):588-599. doi:10.1176/appi.ajp.2015.15070907

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Downloaded from jamanetwork.com by Adiel Ismail on 12/01/2025

33. *Guidance in Authorizing Cannabis Products Within Primary Care*. The College of Family Physicians of Canada; March 2021. Accessed August 15, 2025. https://www.cfpc.ca/CFPC/media/PDF/CFPC-Guidance-in-Cannabis-Within-Primary-Care.pdf

34. *Public Policy Statement on Cannabis*. American Society of Addiction Medicine; 2020. Accessed August 15, 2025. https://downloads.asam.org/sitefinity-production-blobs/docs/default-source/public-policy-statements/2020-public-policy-statement-on-cannabis---reaffirmed-thru-12-12-30.pdf?sfvrsn=6e63f8ca_2

35. Page RL II, Allen LA, Kloner RA, et al; American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. 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

36. Fitzcharles MA, Niaki OZ, Hauser W, Hazlewood G; Canadian Rheumatology Association. Position statement: a pragmatic approach for medical cannabis and patients with rheumatic diseases. *J Rheumatol*. 2019;46(5):532-538. doi:10.3899/jrheum.181120

37. *Sativex*. GW Pharmaceuticals Ltd; 2023. March 30, 2012. Accessed August 15, 2025. https://pdf.hres.ca/dpd_pm/00016162.PDF

38. Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada. 2018. Accessed July 11, 2025. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html

39. Russell K, Cahill M, Duderstadt KG. Medical marijuana guidelines for practice: health policy implications. *J Pediatr Health Care*. 2019;33(6):722-726. doi:10.1016/j.pedhc.2019.07.010

40. Position statement on impact of cannabis on children and adolescents. American Psychiatric Association. 2020. Accessed July 25, 2025. https://johnnysambassadors.org/wp-content/uploads/2022/01/Position-Cannabis-Impact-Children-Adolescents.pdf

41. Bertram JR, Porath A, Seitz D, et al. Canadian guidelines on cannabis use disorder among older adults. *Can Geriatr J*. 2020;23(1):135-142. doi:10.5770/cgj.23.424

42. A guide to cannabis for older adults. Canadian Centre on Substance Use and Addiction. 2020. Accessed September 1, 2025. https://www.ccsa.ca/sites/default/files/2020-07/CCSA-Cannabis-Use-Older-Adults-Guide-2020-en.pdf

43. Allan GM, Ramji J, Perry D, et al. Simplified guideline for prescribing medical cannabinoids in primary care. *Can Fam Physician*. 2018;64(2):111-120.

44. Stott C, White L, Wright S, Wilbraham D, Guy G. A phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of rifampicin, ketoconazole, and omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *Springerplus*. 2013;2(1):236. doi:10.1186/2193-1801-2-236

45. Ho JJY, Goh C, Leong CSA, Ng KY, Bakhtiar A. Evaluation of potential drug-drug interactions with medical cannabis. *Clin Transl Sci*. 2024;17(5):e13812. doi:10.1111/cts.13812

46. Nachnani R, Knehans A, Neighbors JD, et al. Systematic review of drug-drug interactions of delta-9-tetrahydrocannabinol, cannabidiol, and *Cannabis*. *Front Pharmacol*. 2024;15:1282831. doi:10.3389/fphar.2024.1282831

47. Burnett GM, Gorelick DA, Hill KP. Policy ahead of the science: medical cannabis laws versus scientific evidence. *Psychiatr Clin North Am*. 2022; 45(3):347-373. doi:10.1016/j.psc.2022.05.002

48. Gelberg L, Beck D, Koerber J, et al. Cannabis use reported by patients receiving primary care in a large health system. *JAMA Netw Open*. 2024;7(6): e2414809. doi:10.1001/jamanetworkopen.2024.14809

49. 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

50. Chow R, Basu A, Kaur J, et al. Efficacy of cannabinoids for the prophylaxis of chemotherapy-induced nausea and vomiting—a systematic review and meta-analysis. *Support Care Cancer*. 2025;33(3):193. doi:10.1007/s00520-025-09251-w

51. Badowski ME, Perez SE. Clinical utility of dronabinol in the treatment of weight loss associated with HIV and AIDS. *HIV AIDS (Auckl)*. 2016;8:37-45. doi:10.2147/HIV.S81420

52. Kanters S, Renaud F, Rangaraj A, et al. Evidence synthesis evaluating body weight gain among people treating HIV with antiretroviral therapy—a systematic literature review and network meta-analysis. *EClinicalMedicine*. 2022;48:101412. doi:10.1016/j.eclinm.2022.101412

53. 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

54. Mücke M, Weier M, Carter C, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. *J Cachexia Sarcopenia Muscle*. 2018;9(2):220-234. doi:10.1002/jcsm.12273

55. AES position statement on cannabis as a treatment for patients with epileptic seizures. American Epilepsy Society. September 16, 2022. Accessed July 25, 2025. https://aesnet.org/about/about-aes/position-statements/aes-position-statement-on-cannabis-as-a-treatment-for-patients-with-epileptic-seizures

56. AAN position. Use of medical cannabis for neurologic disorders. American Academy of Neurology; 2020. Accessed July 25, 2025. https://www.aan.com/advocacy/medical-cannabis-position-statement

57. Ong MJY, Abd Rahman MSH, Lee VLL, et al. The use of cannabidiol as adjunctive therapy in adult patients with drug-resistant epilepsy: a systematic review and meta-analysis. *Ther Adv Neurol Disord*. 2025;18:17562864251313914. doi:10.1177/17562864251313914

58. IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia. International association for the study of pain presidential task force on cannabis and cannabinoid analgesia position statement. *Pain*. 2021;162(suppl 1):S1-S2. doi:10.1097/j.pain.0000000000002265

59. Living systematic review on cannabis and other plant-based treatments for chronic pain. Agency for Healthcare Research and Quality. August 4, 2024. Accessed July 5, 2025. https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review

60. Verduzco-Gutierrez M, Raghavan P, Pruente J, et al. AAPM&R consensus guidance on spasticity assessment and management. *PM R*. 2024;16(8): 864-887. doi:10.1002/pmrj.13211

61. Sativex for moderate to severe spasticity in multiple sclerosis (MS)-prescribing guideline in primary care. National Health Service Accessed October 6, 2025. https://nclhealthandcare.org.uk/wp-content/uploads/2023/09/SCG_Sativex.pdf

62. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG; MUSEC Research Group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry*. 2012; 83(11):1125-1132. doi:10.1136/jnnp-2012-302468

63. Zajicek J, Fox P, Sanders H, et al; UK MS Research Group. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet*. 2003;362(9395): 1517-1526. doi:10.1016/S0140-6736(03)14738-1

64. Häuser W, Welsch P, Radbruch L, Fisher E, Bell RF, Moore RA. Cannabis-based medicines and medical cannabis for adults with cancer pain. *Cochrane Database Syst Rev*. 2023;6(6):CD014915.

65. Morin CM, Inoue Y, Kushida C, Poyares D, Winkelman J; Guidelines Committee Members; Governing Council of the World Sleep Society. Endorsement of European guideline for the diagnosis and treatment of insomnia by the World Sleep Society. *Sleep Med*. 2021;81:124-126. doi:10.1016/j.sleep.2021.01.023

66. Insomnia guideline. Kaiser Permanente. 2021. Accessed July 5, 2025. https://wa-provider.kaiserpermanente.org/static/pdf/

67. AminiLari M, Wang L, Neumark S, et al. Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials. *Sleep*. 2022;45(2):zsab234. doi:10.1093/sleep/zsab234

68. Bosnjak Kuharic D, Markovic D, Brkovic T, et al. Cannabinoids for the treatment of dementia. *Cochrane Database Syst Rev*. 2021;9(9):CD012820.

69. Position statement in opposition to cannabis as medicine. American Psychiatric Association. 2019. Accessed August 15, 2025. https://www.psychiatry.org/getattachment/12aa44f8-016e-4f8c-8b92-d3fb11a7155f/Position-Cannabis-as-Medicine.pdf

70. Hill KP, Gold MS, Nemeroff CB, et al. Risks and benefits of cannabis and cannabinoids in psychiatry. *Am J Psychiatry*. 2022;179(2):98-109. doi:10.1176/appi.ajp.2021.21030320

71. Maggu G, Choudhary S, Jaishy R, Chaudhury S, Saldanha D, Borasi M. Cannabis use and its relationship with bipolar disorder: a systematic review and meta-analysis. *Ind Psychiatry J*. 2023;32(2):202-214. doi:10.4103/ipj.ipj_43_23

72. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis.

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Schizophr Bull. 2016;42(5):1262-1269. doi:10.1093/schbul/sbw003

73. Vaucher J, Keating BJ, Lasserre AM, et al. Cannabis use and risk of schizophrenia: a Mendelian randomization study. *Mol Psychiatry*. 2018;23(5):1287-1292. doi:10.1038/mp.2016.252

74. Sorkhou M, Dent EL, George TP. Cannabis use and mood disorders: a systematic review. *Front Public Health*. 2024;12:1346207. doi:10.3389/fpubh.2024.1346207

75. Shamabadi A, Ahmadzade A, Pirahesh K, Hasanzadeh A, Asadigandomani H. Suicidality risk after using cannabis and cannabinoids: an umbrella review. *Dialogues Clin Neurosci*. 2023;25(1):50-63. doi:10.1080/19585969.2023.2231466

76. VA/DoD clinical practice guideline for management of posttraumatic stress disorder and acute stress disorder. US Department of Veterans Affairs. 2023. Accessed August 15, 2025. https://www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG-Edited-111624-V5-81825.pdf

77. Bonn-Miller MO, Sisley S, Riggs P, et al. The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: a randomized cross-over clinical trial. *PLoS One*. 2021;16(3):e0246990. doi:10.1371/journal.pone.0246990

78. Han K, Wang JY, Wang PY, Peng YCH. Therapeutic potential of cannabidiol (CBD) in anxiety disorders: a systematic review and meta-analysis. *Psychiatry Res*. 2024;339:116049. doi:10.1016/j.psychres.2024.116049

79. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res*. 2006;39(4):421-429. doi:10.1590/S0100-879X2006000400001

80. Gazendam A, Nucci N, Gouveia K, Abdel Khalik H, Rubinger L, Johal H. Cannabinoids in the management of acute pain: a systematic review and meta-analysis. *Cannabis Cannabinoid Res*. 2020;5(4):290-297. doi:10.1089/can.2019.0079

81. Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol*. 1981;21(S1):320S-326S. doi:10.1002/j.1552-4604.1981.tb02610.x

82. Nielsen S, Picco L, Murnion B, et al. Opioid-sparing effect of cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies. *Neuropsychopharmacology*. 2022;47(7):1315-1330. doi:10.1038/s41386-022-01322-4

83. Urbi B, Corbett J, Hughes I, et al. Effects of cannabis in Parkinson's disease: a systematic review and meta-analysis. *J Parkinsons Dis*. 2022;12(2):495-508. doi:10.3233/JPD-212923

84. Turbert D, Gudgel D. Does marijuana help treat glaucoma or other eye conditions? American Academy of Ophthalmology. December 13, 2023. Accessed July 2, 2025. https://www.aao.org/eye-health/tips-prevention/medical-marijuana-glaucoma-treament

85. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology*. 1980;87(3):222-228. doi:10.1016/S0161-6420(80)35258-5

86. Nielsen S, Murnion B, Campbell G, Young H, Hall W. Cannabinoids for the treatment of spasticity. *Dev Med Child Neurol*. 2019;61(6):631-638. doi:10.1111/dmcn.14165

87. Andrews CN, Devlin SM, Le Foll B, et al. Canadian Association of Gastroenterology position statement: use of cannabis in gastroenterological and hepatic disorders. *J Can Assoc Gastroenterol*. 2019;2(1):37-43. doi:10.1093/jcag/gwy064

88. Kang H, Schmoyer CJ, Weiss A, Lewis JD. Meta-analysis of the therapeutic impact of cannabinoids in inflammatory bowel disease. *Inflamm Bowel Dis*. 2025;31(2):450-460. doi:10.1093/ibd/izae158

89. Marchand G, Masoud AT, Govindan M, et al. Birth outcomes of neonates exposed to marijuana in utero: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(1):e2145653. doi:10.1001/jamanetworkopen.2021.45653

90. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem*. 2013;59(3):478-492. doi:10.1373/clinchem.2012.194381

91. Jin A, Darzi AJ, Dargham A, et al. Cannabis consumption and motor vehicle collision: a systematic review and meta-analysis of observational studies. *Int J Drug Policy*. 2025;142:104832. doi:10.1016/j.drugpo.2025.104832

92. Petrilli K, Hines L, Adams S, Morgan CJ, Curran HV, Freeman TP. High potency cannabis use, mental health symptoms and cannabis dependence: triangulating the evidence. *Addict Behav*. 2023;144:107740. doi:10.1016/j.addbeh.2023.107740

93. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182(14):E694-E701. doi:10.1503/cmaj.091414

94. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

95. Scott JC, Slomiak ST, Jones JD, Rosen AFG, Moore TM, Gur RC. Association of cannabis with cognitive functioning in adolescents and young adults: a systematic review and meta-analysis. *JAMA Psychiatry*. 2018;75(6):585-595. doi:10.1001/jamapsychiatry.2018.0335

96. Figueiredo PR, Tolomeo S, Steele JD, Baldacchino A. Neurocognitive consequences of chronic cannabis use: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2020;108:358-369. doi:10.1016/j.neubiorev.2019.10.014

97. Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol*. 2012;20(5):420-429. doi:10.1037/a0029117

98. Jeffers AM, Glantz S, Byers AL, Keyhani S. Association of cannabis use with cardiovascular outcomes among US adults. *J Am Heart Assoc*. 2024;13(5):e030178. doi:10.1161/JAHA.123.030178

99. Braymiller JL, Barrington-Trimis JL, Leventhal AM, et al. Assessment of nicotine and cannabis vaping and respiratory symptoms in young adults. *JAMA Netw Open*. 2020;3(12):e2030189. doi:10.1001/jamanetworkopen.2020.30189

100. Habboushe J, Rubin A, Liu H, Hoffman RS. The prevalence of cannabinoid hyperemesis syndrome among regular marijuana smokers in an urban public hospital. *Basic Clin Pharmacol Toxicol*. 2018;122(6):660-662. doi:10.1111/bcpt.12962

101. Rubio-Tapia A, McCallum R, Camilleri M. AGA clinical practice update on diagnosis and management of cannabinoid hyperemesis syndrome. *Gastroenterology*. 2024;166(5):930-934.e1. doi:10.1053/j.gastro.2024.01.040

102. Bahji A, Stephenson C, Tyo R, Hawken ER, Seitz DP. Prevalence of cannabis withdrawal symptoms among people with regular or dependent use of cannabinoids: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(4):e202370. doi:10.1001/jamanetworkopen.2020.2370

103. Connor JP, Stjepanović D, Budney AJ, Le Foll B, Hall WD. Clinical management of cannabis withdrawal. *Addiction*. 2022;117(7):2075-2095. doi:10.1111/add.15743

104. Dawson D, Stjepanović D, Lorenzetti V, Cheung C, Hall W, Leung J. The prevalence of cannabis use disorders in people who use medicinal cannabis: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2024;257:111263. doi:10.1016/j.drugalcdep.2024.111263

105. Storck W, Elbaz M, Vindis C, Déguilhem A, Lapeyre-Mestre M, Jouanjus E. Cardiovascular risk associated with the use of cannabis and cannabinoids: a systematic review and meta-analysis. *Heart*. Published online June 17, 2025. doi:10.1136/heartjnl-2024-325429

106. Kamel I, Mahmoud AK, Twayana AR, Younes AM, Horn B, Dietzius H. Myocardial infarction and cardiovascular risks associated with cannabis use: a multicenter retrospective study. *JACC Adv*. 2025;4(5):101698. doi:10.1016/j.jacadv.2025.101698

107. Sagris M, Antonopoulos AS, Theofilis P, et al. Risk factors profile of young and older patients with myocardial infarction. *Cardiovasc Res*. 2022;118(10):2281-2292. doi:10.1093/cvr/cvab264

108. Cheung CP, Coates AM, Baker RE, Burr JF. Acute effects of cannabis inhalation on arterial stiffness, vascular endothelial function, and cardiac function. *J Am Heart Assoc*. 2024;13(23):e037731. doi:10.1161/JAHA.124.037731

109. Mohammadi L, Navabzadeh M, Jiménez-Téllez N, et al. Association of endothelial dysfunction with chronic marijuana smoking and THC-edible use. *JAMA Cardiol*. 2025;10(8):851-855. doi:10.1001/jamacardio.2025.1399

110. Therapeutic Effects of cannabis and cannabinoids. In: *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. National Academies Press; 2017. Accessed July 2, 2025. https://www.ncbi.nlm.nih.gov/books/NBK425767/

111. Saavedra MS, Thota P, Peresuodei TS, et al. Neurocognitive impact of exposure to cannabis concentrates and cannabinoids including vaping in children and adolescents: a systematic review. *Cureus*. 2024;16(1):e52362. doi:10.7759/cureus.52362

112. Malvi A, Khatib MN, Balaraman AK, et al. Cannabis consumption and risk of asthma: a systematic review and meta-analysis. *BMC Pulm Med*. 2025;25(1):48. doi:10.1186/s12890-025-03516-0

113. Ghasemiesfe M, Ravi D, Vali M, et al. Marijuana use, respiratory symptoms, and pulmonary function: a systematic review and meta-analysis. *Ann Intern Med*. 2018;169(2):106-115. doi:10.7326/M18-0522

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114. Myran DT, Pugliese M, Harrison LD, Stall NM, Webber C. Risk of dementia in individuals with emergency department visits or hospitalizations due to cannabis. *JAMA Neurol*. 2025;82(6):570-579. doi:10.1001/jamaneurol.2025.0530

115. 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

116. Gagnon M, McRitchie T, Montsion K, et al. High levels of pesticides found in illicit cannabis inflorescence compared to licensed samples in Canadian study using expanded 327 pesticides multiresidue method. *J Cannabis Res*. 2023;5(1):34. doi:10.1186/s42238-023-00200-0

117. Gardener H, Wallin C, Bowen J. Heavy metal and phthalate contamination and labeling integrity in a large sample of US commercially available cannabidiol (CBD) products. *Sci Total Environ*. 2022;851(pt 1):158110. doi:10.1016/j.scitotenv.2022.158110

118. Le Q, Dangol G, Bhandari A. A rare case of diffuse alveolar hemorrhage caused by fentanyl-laced marijuana. *Cureus*. 2023;15(5):e38523. doi:10.7759/cureus.38523

119. Giordano G, Brook CP, Ortiz Torres M, et al. Accuracy of labeled THC potency across flower and concentrate cannabis products. *Sci Rep*. 2025;15(1):20822. doi:10.1038/s41598-025-03854-3

120. Geweda MM, Majumdar CG, Moore MN, et al. Evaluation of dispensaries' cannabis flowers for accuracy of labeling of cannabinoids content. *J Cannabis Res*. 2024;6(1):11. doi:10.1186/s42238-024-00220-4

121. Gidal BE, Vandrey R, Wallin C, et al. Product labeling accuracy and contamination analysis of commercially available cannabidiol product samples. *Front Pharmacol*. 2024;15:1335441. doi:10.3389/fphar.2024.1335441

122. Troup LJ, Erridge S, Ciesluk B, Sodergren MH. Perceived stigma of patients undergoing treatment with cannabis-based medicinal products. *Int J Environ Res Public Health*. 2022;19(12):7499. doi:10.3390/ijerph19127499

123. Webster LR, Fine PG. Approaches to improve pain relief while minimizing opioid abuse liability. *J Pain*. 2010;11(7):602-611. doi:10.1016/j.jpain.2010.02.008

124. Wilsey B, Atkinson JH, Marcotte TD, Grant I. The medicinal cannabis treatment agreement: providing information to chronic pain patients via a written document. *Clin J Pain*. 2015;31(12):1087-1096. doi:10.1097/AJP.0000000000000145

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