Medical Cannabis: An Evidence-Based Review of Therapeutic Applications and Clinical Considerations

I. Introduction to Medical Cannabis

Historical Context and Current Landscape

The medicinal use of *Cannabis sativa L.* boasts a rich history spanning thousands of years, with ancient civilizations such as the Chinese and Egyptians recognizing its pain-relieving, anti-inflammatory, and calming properties.[1] This long-standing traditional use underscores an early appreciation for its therapeutic potential. However, the last century witnessed a significant shift in perception, largely driven by concerns over its psychotropic and abusive effects, leading to widespread prohibition and a negative public image in many countries.[3]

In recent years, a re-evaluation of cannabis for medical purposes has gained momentum globally, leading to its legalization in several nations and numerous U.S. states. This resurgence of interest has been fueled by increased media attention and anecdotal reports of effectiveness, although the scientific evidence supporting these claims is still evolving.[3] The historical trajectory of cannabis, moving from ancient therapeutic recognition to modern prohibition and then a contemporary resurgence of interest, illustrates a cyclical pattern in how society and legal frameworks respond to complex botanical medicines. This dynamic interplay suggests that regulatory and societal structures often lag behind the evolving scientific understanding of cannabis and the growing demand from patients, creating a challenging and often fragmented landscape for both research and patient access.

Clarifying "Treatment" vs. "Cure" in Medical Cannabis

A fundamental distinction must be established when discussing the role of medical cannabis: it primarily serves as a *treatment* for symptoms or conditions, offering relief or management, rather than a *cure* for any disease.[4] The U.S. Food and Drug Administration (FDA) has not approved the

marijuana plant itself to treat any medical conditions.[4] FDA approval signifies that a drug's benefits have been rigorously reviewed and determined to outweigh its known and potential risks for the intended patient population.[4]

While a "strong and growing consensus" exists within the scientific community regarding the *therapeutic benefits* of cannabis, particularly as a palliative adjunct in cancer care and with potential anticarcinogenic effects, this recognition does not equate to a curative claim.[6] The consistent differentiation between "treatment" and "cure" for cannabis underscores a critical scientific and regulatory imperative for robust evidence. The FDA's approach, focusing on the approval of specific, purified cannabinoid compounds rather than the whole plant, highlights a stringent, evidence-based pathway to drug approval that stands in contrast to broader public perceptions and state-level medical cannabis programs. This approach indicates that while the cannabis plant contains components with therapeutic promise, the lack of standardization, consistent dosing, and large-scale, controlled clinical trials for the

plant itself currently prevent its federal approval as a medicine.

Overview of FDA-Approved Cannabis-Derived Medications

The FDA has not approved the *marijuana plant* for medical purposes.[4] However, it has approved certain purified substances derived from cannabis, referred to as analogs, which have undergone rigorous testing and met pharmaceutical standards.[4]

These FDA-approved cannabis-derived medications include:

- **Cannabidiol (Epidiolex®):** This purified analog is approved to prevent and control seizures in individuals with Lennox-Gastaut syndrome or Dravet syndrome, two rare and severe forms of epilepsy.[4] It is a prescription medication and differs from over-the-counter CBD products.[4] Notably, Epidiolex does not contain

tetrahydrocannabinol (THC) and therefore does not produce euphoric effects.[8]

- **Dronabinol (Marinol®, Syndros) and Nabilone (Cesamet®):** These are synthetic forms of THC. They are approved to prevent and treat nausea and vomiting related to chemotherapy (CINV).[4] Additionally, Dronabinol can help treat loss of appetite and weight loss in people with HIV or AIDS, and it may also manage agitation in individuals with severe dementia.[4]

The FDA's selective approval of purified or synthetic cannabis-derived compounds, while maintaining a Schedule I classification for the cannabis plant, highlights a significant regulatory and scientific paradox. This indicates that the therapeutic efficacy of cannabinoids is acknowledged when isolated and subjected to stringent pharmaceutical validation. However, the complex, variable composition and uncontrolled delivery methods of the whole plant present substantial hurdles to its broader medical acceptance and regulation. This dichotomy underscores the ongoing challenge of integrating a historically used botanical medicine into modern, evidence-based pharmacotherapy.

Table 1: FDA-Approved Cannabis-Derived Medications and Their Indications

Medication Name (Brand & Generic)	Active Cannabinoid(s)	FDA-Approved Condition(s)	Key Characteristics
Epidiolex® (Cannabidiol)	Cannabidiol (CBD)	Lennox-Gastaut syndrome, Dravet syndrome (rare forms of epilepsy)	Purified, plant-derived, prescription, non-psychoactive
Marinol® (Dronabinol), Syndros	Tetrahydrocannabinol (THC)	Chemotherapy-induced nausea and vomiting (CINV), Appetite loss and weight loss in HIV/AIDS, Agitation in severe dementia	Synthetic, prescription
Cesamet® (Nabilone)	Tetrahydrocannabinol (THC) analog	Chemotherapy-induced nausea and vomiting (CINV)	Synthetic, prescription

II. The Endocannabinoid System and Cannabis Pharmacology

Understanding the Endocannabinoid System (ECS)

The endocannabinoid system (ECS) is a complex internal homeostatic system found in all vertebrates, playing a pivotal role in maintaining physiological balance.[9] This intricate system is deeply involved in the nervous system and regulates a multitude of vital processes throughout the body. These include appetite, digestion, mood, coordination, immunomodulation, cardiovascular functions, sensory integration, tumor surveillance, fertility, bone physiology, the hypothalamic-pituitary-adrenal axis, and neural development.[9] Furthermore, the ECS has been shown to affect the urologic and reproductive systems.[10]

The discovery of the ECS has provided a scientific explanation for how cannabis phytoconstituents interact with and affect human physiology, particularly the immune system and the central nervous system.[1] The widespread involvement of the ECS in such diverse physiological processes suggests that cannabis, by interacting with this fundamental system, possesses the potential for broad, pleiotropic effects across multiple body systems. This extensive influence explains why cannabis is being explored for such a wide array of medical conditions. However, this broad interaction also implies a complex risk-benefit profile, as modulating such a pervasive system can lead to unintended or off-target effects, necessitating careful consideration of its therapeutic application.

Key Cannabinoids: Tetrahydrocannabinol (THC) and Cannabidiol (CBD) – Mechanisms and Effects

Cannabis contains a variety of compounds, with at least 104 unique to the plant, known as phytocannabinoids.[9] These compounds interact with endocannabinoid receptors or influence the ECS through non-receptor mediated pathways. The two most extensively studied cannabinoids are Tetrahydrocannabinol (THC) and Cannabidiol (CBD).

Tetrahydrocannabinol (THC)

THC (Δ9-tetrahydrocannabinol) acts as a partial agonist at human cannabinoid receptors, specifically CB1 and CB2 receptors.[11] CB1 receptors are predominantly located in the central nervous system (CNS) and are crucial for modulating pain, cognition, memory, reward sensation, emotional behavior, sensory perception, and motor control.[9] THC's analgesic effects are largely mediated through its action on CB1 receptors.[11]

The therapeutic effects attributed to THC include the reduction of nausea and vomiting, stimulation of appetite, reduction of pain and inflammation, and an increase in muscle relaxation.[9] However, THC is also responsible for the psychotropic effects associated with cannabis, such as euphoria, altered perception, and impaired verbal fluency and working memory.[13] Potential adverse effects of THC include dizziness, somnolence, dry mouth, disorientation, anxiety, and acute psychosis, particularly with high doses or in individuals predisposed to mental health conditions.[4] High doses of THC can even trigger schizophrenia-like symptoms.[13]

Cannabidiol (CBD)

CBD is a non-psychoactive component of cannabis, meaning it does not produce the "high" associated with THC.[8] While CBD has a low affinity for CB1 and CB2 receptors, it interacts with a variety of other molecular targets, including serotonin 5-HT1a receptors, transient receptor potential (TRP) channels, and peroxisome proliferator-activated receptors (PPARs).[3]

CBD's therapeutic potential spans several areas, including the treatment of insomnia [16], anti-epileptic properties [18], anti-inflammatory and antioxidant activity.[18] It has also been observed to reduce nausea via a 5-HT1A mechanism.[17] Furthermore, CBD can antagonize some of the unwanted psychoactive effects of THC, such as intoxication, sedation, tachycardia, and anxiety.[12] Common adverse effects specifically associated with the FDA-approved CBD medication Epidiolex include drowsiness, diarrhea, decreased appetite, fatigue, sleep problems, and elevated liver enzymes.[8]

CB2 Receptors

Beyond CB1, CB2 receptors are primarily immunomodulatory and anti-inflammatory.[9] They represent a promising target for therapeutic interventions in chronic inflammatory diseases, neuropathic pain, and neurodegenerative disorders.[11]

The distinct yet often synergistic roles of THC and CBD, alongside other minor

cannabinoids and terpenes (which contribute to what is known as the "entourage effect"), indicate that the therapeutic efficacy of cannabis is highly dependent on the specific cannabinoid profile of the product and the individual patient's characteristics. This inherent complexity necessitates a personalized medicine approach, moving beyond a simplistic view of "marijuana" as a single, uniform drug. Understanding these intricate interactions is crucial for optimizing treatment outcomes and minimizing adverse effects, posing significant challenges for standardized research and product development in the field of medical cannabis.

III. Conditions with Established or Emerging Therapeutic Benefit

Chronic Pain (including Neuropathic Pain)

Chronic pain is a persistent and often debilitating condition that can be severe or intractable, frequently stemming from nerve damage (neuropathic pain) associated with conditions such as HIV or diabetes, or from rheumatic disorders.[4] Historically, cannabis has been recognized for its pain-relieving properties.[1] The endocannabinoid system, particularly CB1 receptors located in both the central nervous system and peripheral tissues, plays a significant role in pain perception and modulation.[9] THC, acting as a CB1 agonist, contributes to analgesic effects by modulating neuronal activity.[11] Cannabinoids have also been shown to attenuate capsaicin-evoked hyperalgesia.[21]

There is "conclusive or substantial evidence" supporting the effectiveness of cannabis-based products for the treatment of chronic pain in adults.[9] However, the evidence is not uniformly strong across all forms of pain or administration methods. A 2021 review, for instance, found "little effect of using non-inhaled cannabis to relieve chronic pain".[16] Similarly, a 2019 systematic review reported inconsistent results for neuropathic pain, muscle spasms associated with multiple sclerosis, and pain from rheumatic disorders, and found cannabis was

not effective in treating chronic cancer pain.[16] This apparent contradiction—between broad claims of substantial evidence and more specific findings of limited or

inconsistent efficacy—highlights that the effectiveness of cannabis for pain is highly dependent on the type of pain, the method of administration, and the specific cannabinoid profile. This observation underscores the need for highly targeted research and personalized treatment plans, rather than a generalized recommendation for all chronic pain conditions.

Inhaled cannabis can provide faster pain relief, with effects peaking within three minutes and achieving an analgesic effect in approximately seven minutes.[16] Clinical trials have shown a modest reduction in pain with cannabinoids, including THC, compared to placebo (e.g., a 37% reduction versus 31% with placebo, or an average reduction of -0.41 on a 10-point pain scale).[11] This suggests that cannabis can serve as a complementary treatment.[11] For neuropathic pain, results have been promising but inconsistent; for example, patients with HIV-associated sensory neuropathy reported more than a 30% pain reduction with inhaled cannabis (52% of the cannabis group versus 24% of the placebo group).[11] Dose-dependent pain reduction has also been observed in studies involving diabetic neuropathy.[11] Orally administered dronabinol (at doses ranging from 10 mg to 15 mg) significantly reduced reported pain levels, with patients reporting an average reduction of 5.3 on a visual analog pain scale.[11]

THC is considered the primary component for analgesic effects through its CB1 receptor modulation.[11] While CBD also possesses anti-inflammatory properties [18], its specific role in pain relief is less clearly delineated in the provided information. However, THC:CBD extracts have demonstrated efficacy for pain relief in advanced cancer pain that was not fully relieved by strong opioids.[14] It is important to note that cannabis provides symptomatic pain relief and is not a cure for chronic pain or its underlying causes. Side effects can include dizziness, somnolence, dry mouth, disorientation, anxiety, and acute psychosis.[9] Despite these, cannabis is generally considered safe and appears to be safer than opioids in palliative care settings.[16] Long-term use, however, may lead to cannabis use disorder (CUD).[1] General dosage recommendations emphasize a "start low and go slow" approach.[22]

Chemotherapy-Induced Nausea and Vomiting (CINV)

Chemotherapy-induced nausea and vomiting (CINV) represents a significant challenge for cancer patients, severely impacting their quality of life, compliance with treatment, and potentially leading to metabolic imbalances, nutrient depletion, and

anorexia.[24] CINV can manifest in various forms: acute (within 24 hours of treatment), delayed (after 24 hours), anticipatory (occurring before treatment due to prior negative experiences), or refractory (unresponsive to prophylactic antiemetics).[24]

Cannabinoids are understood to prevent chemotherapy-induced emesis by acting at central CB1 receptors, thereby preventing the proemetic effects of endogenous compounds such as dopamine and serotonin.[24] CBD, in particular, reduces nausea through a 5-HT1A receptor mechanism, suppressing serotonin elevation in the interoceptive insular cortex, a brain region implicated in triggering nausea.[17] Cannabidiolic acid (CBDA), the acidic precursor to CBD found in the fresh cannabis plant, has shown even greater potency (1000 to 10,000 times) than CBD in reducing nausea and vomiting via the 5-HT1A pathway.[17]

Medical cannabis is considered "somewhat effective" in managing CINV and may be a "reasonable option" for patients who do not respond to conventional preferential treatments.[16] Comparative studies have found cannabinoids to be more effective than some traditional antiemetics, such as prochlorperazine, promethazine, and metoclopramide, although they are associated with a higher side-effect profile, including dizziness, dysphoria, and hallucinations.[16] The FDA has approved Dronabinol (Marinol®, Syndros) and Nabilone (Cesamet®), which are synthetic forms of THC, specifically for the treatment of CINV.[4] Research indicates conclusive or substantial evidence supporting the use of oral cannabinoids as antiemetics in CINV.[9] Studies have reported significant relief from CINV, with 70-100% of patients experiencing relief from nausea and vomiting when smoking cannabis, and 76-88% with oral THC capsules.[24] Preclinical models have shown CBD (at 5 mg/kg, IP) to effectively reduce chemotherapy-induced vomiting and acute/anticipatory nausea.[17]

While THC is effective, it can induce sedation and intoxication, which may or may not be desirable for patients.[17] CBD is effective at lower doses (0.5-5.0 mg/kg), but higher doses can paradoxically become ineffective or even potentiate vomiting.[17] CBDA demonstrates high potency for anti-nausea effects.[17] It is important to emphasize that cannabis provides symptomatic relief from nausea and vomiting and is not a cure for cancer. Side effects can include dizziness, dysphoria, hallucinations, drowsiness, altered moods, and increased appetite.[16] Common adverse events for dronabinol include anxiety, confusion, somnolence, and thinking abnormalities.[17] Short-term side effects for smoked marijuana include sedation, a "high," and smoke intolerance.[24] Dronabinol typically has an onset of action within 0.5-1 hour, with peak effects at 2-4 hours, lasting 4-6 hours.[24]

Epilepsy and Seizure Disorders (Focus on Lennox-Gastaut and Dravet Syndromes)

Epilepsy and seizure disorders are neurological conditions characterized by recurrent seizures. Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) are particularly severe and rare forms of childhood epilepsy, often presenting with varied seizure subtypes, severity, and frequency, sometimes leading to hundreds of seizures daily.[4]

The exact anticonvulsant mechanism of cannabidiol (CBD) is still largely under investigation, but it is theorized to reduce seizure severity and frequency through a multifactorial modulation of various neurochemicals and pathways, including serotonin, gamma-amino butyric acid (GABA), T-type calcium channels, and N-methyl-D-aspartate (NMDA).[18] CBD has a low affinity for the classical CB1 and CB2 receptors.[18] Recent animal studies suggest that CBD may preferentially target resurgent sodium currents from mutant channels, which are observed in syndromic epilepsies like Dravet syndrome.[18]

A significant development in this area is the FDA approval of Epidiolex® (cannabidiol) oral solution for treating seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients aged 2 years or older.[4] This approval was based on conclusive scientific evidence derived from rigorous double-blind, randomized, placebo-controlled trials.[8] All four pivotal clinical trials (GWPCARE 1-4) for Epidiolex consistently demonstrated a significant absolute reduction in seizure frequency.[8] While Epidiolex is currently approved for this "narrow niche" of rare syndromes, there is a growing trend of off-label use for other medically refractory epilepsies.[18] It is important to note that, generally, "it's not clear if marijuana effectively treats seizures" [5], which highlights the crucial distinction between the efficacy of a purified CBD compound and the whole cannabis plant.

CBD is the active compound in Epidiolex. It is non-psychoactive and does not induce euphoria or addiction.[8] Current evidence does not support CBD as a monotherapy for epilepsy; it is typically used as an adjunct therapy alongside standard anti-epileptic drugs.[18] Epidiolex is considered a "treatment" for these forms of epilepsy, not a cure.[5] The most common adverse effects (≥10%) reported for Epidiolex in clinical trials include somnolence, fatigue, rash, decreased appetite, diarrhea, insomnia, infection, and elevated transaminases (liver enzymes).[8] Elevated liver enzymes, particularly when used concomitantly with valproate, may necessitate treatment discontinuation.[15] Furthermore, CBD is a potent inhibitor of cytochrome P450 enzymes (CYP2C19 and

3A4, and to a lesser extent CYP2D6), leading to potential drug interactions with numerous medications, including other anti-epileptic drugs like clobazam.[4]

Multiple Sclerosis (MS) and Spasticity

Multiple sclerosis (MS) is a chronic neurological disorder characterized by damage to the nervous system, which can result in uncontrolled limb motor function, leading to painful muscle stiffness or spasms (spasticity) and exaggerated tendon reflexes.[5]

Cannabinoids, particularly THC, act as partial agonists at both CB1 and CB2 receptors, modulating the balance between excitatory neurotransmitters like glutamic acid and inhibitory neurotransmitters like gamma-aminobutyric acid (GABA).[12] This modulation leads to muscle relaxation and an improvement in spasticity.[12] Specifically, an FDA-approved cannabis-derived medication, Sativex (nabiximols), has been shown to modulate cortical excitability by increasing intracortical inhibition and reducing spinal excitability, contributing to spasticity improvement.[12]

Oral cannabis extract has demonstrated effectiveness in reducing patient-centered measures of spasticity.[9] A trial of cannabis is considered a reasonable option for spasticity if other treatments have not been effective.[16] Its use for MS is approved in ten countries.[16] Sativex, an oromucosal spray containing a 1:1 ratio of THC and CBD, is recognized as an effective add-on option for moderate to severe spasticity in MS patients who have not responded adequately to existing therapies.[12] Clinical trials have reported significant improvements in both subjective and objective measures of spasticity, as well as improvements in ambulation, pain, the frequency of daily spasms, and incontinence episodes after a month of nabiximols treatment.[12] In an experimental mouse model of MS, Sativex (at a dose of 10 mg/kg THC + 10 mg/kg CBD) was found to be as effective as baclofen, a common first-line treatment for spasticity, and has shown to be better tolerated than baclofen in other contexts.[20]

THC is the primary active substance responsible for muscle relaxation and spasticity improvement.[12] CBD, while also present in formulations like Sativex, plays a crucial role in modulating some of the undesirable psychoactive effects of THC, such as intoxication, sedation, and anxiety.[12] The combination of THC and CBD in a 1:1 ratio, as found in Sativex, is believed to provide synergistic benefits.[20] Cannabis provides symptomatic relief from spasticity and associated symptoms; it is not a cure for MS. Main side effects reported for Sativex include dizziness, dry mouth, nausea, and

weakness.[12] General marijuana side effects can include headaches, dry mouth and eyes, lightheadedness, dizziness, drowsiness, fatigue, nausea, vomiting, disorientation, hallucinations, increased heart rate, and increased appetite.[5]

Appetite Loss and Wasting Syndrome (Cachexia) in HIV/AIDS and Cancer

Anorexia (loss of appetite) and cachexia (severe muscle loss with or without fat loss) are debilitating conditions frequently observed as end-stage features of diseases such as AIDS and certain metastatic cancers.[4] These syndromes significantly compromise a patient's quality of life and contribute to disease progression.[25]

The cannabinoid receptor type 1 (CB1R) plays a significant role in modulating appetite and satiety through its presynaptic activity on both orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) neurons.[25] Activation of CB1R can lead to increased caloric intake and reduced catabolism.[25] THC, as a partial agonist of CB1R, has been shown to stimulate appetite.[25] Additionally, CBD possesses immunoregulatory functions, particularly through its influence on inflammatory cytokines like TNF-α and interleukin-6, suggesting a potential mechanism to address the inflammatory component of cachexia.[25]

Dronabinol (Marinol®, Syndros) is FDA-approved specifically for the treatment of loss of appetite and weight loss in individuals with HIV or AIDS.[4] It is also approved to manage agitation in severe dementia.[4] Short-term (six-week) and long-term (one-year) therapy with dronabinol in HIV patients has been associated with increased appetite and stable weight.[26] Dronabinol has also been shown to improve appetite and promote weight gain in cancer patients, although this gain is primarily in fat mass.[26]

However, despite THC's clear mechanism for appetite stimulation and Dronabinol's FDA approval for HIV/AIDS-related wasting, a comprehensive systematic review and meta-analysis found no *statistically significant* change in appetite across five studies using cannabis-based medicine for general cachexia.[25] This review also concluded that there is no robust evidence to recommend

any single pharmacological agent for the treatment of cachexia.[25] This critical observation indicates that while cannabis may offer symptomatic relief for appetite loss in some individuals, its overall impact on the complex, multifactorial syndrome of

cachexia might be limited, or the existing research is insufficient to demonstrate robust, consistent efficacy across diverse patient populations and study designs. This highlights the challenge of treating a complex syndrome versus a single symptom and suggests that cachexia likely requires combination therapies.[26]

THC is the primary cannabinoid responsible for appetite stimulation.[25] CBD's immunomodulatory functions may address the inflammatory aspects of cachexia.[25] Combination THC/CBD regimens are suggested to warrant further evaluation.[25] Cannabis provides symptomatic relief (appetite stimulation, weight stabilization) but is not a cure for the underlying diseases. Side effects can include dizziness, dry mouth, hypotension, moderate sedation, euphoria or dysphoria.[26] High THC doses (20mg) can lead to heavy sedation and "depersonalization".[26] Cannabinoids can modulate the immune system, which could be a contraindication in some immunosuppressed cancer patients.[26]

Glaucoma

Glaucoma is an ocular condition characterized by increased pressure within the eye (intraocular pressure, IOP), which can lead to progressive vision loss due to damage to the optic nerve.[5]

Cannabinoids have been shown to effectively lower IOP.[19] Beyond this, they possess neuroprotective properties, including the ability to inhibit glutamate release, block NMDA receptors, and act as antioxidants, all of which can help prevent retinal ganglion cell death.[19] Additionally, cannabinoids exhibit vasorelaxant properties, which theoretically could increase ocular blood flow.[19]

Research indicates that marijuana *might* reduce IOP, but this effect appears to be transient, lasting only a few hours.[5] A critical and potentially counterproductive finding suggests that marijuana may

decrease blood flow to the optic nerve, which could paradoxically *increase the risk for vision loss* in people with glaucoma.[5] This profound contradiction implies that despite a temporary symptomatic benefit in IOP reduction, the overall physiological impact of cannabis on glaucoma could be detrimental, making it an unsuitable primary treatment. This observation underscores the necessity of evaluating the complete therapeutic profile of a substance rather than focusing on isolated effects.

Studies have shown significant lowering of IOP compared to baseline, though not always consistently compared to placebo.[27] Oral dronabinol has been observed to increase optic nerve head blood flow in healthy volunteers without affecting IOP.[27] A sublingual spray containing Δ-9-THC (5 mg) and CBD (20 and 40 mg) demonstrated significant IOP lowering at 2 hours, but notably, the 40mg CBD dose produced a transient

increase in IOP at 4 hours.[27] Furthermore, tolerance to the IOP-reducing effects can develop with chronic cannabis use.[27]

THC is primarily implicated in IOP reduction.[27] CBD's role is complex, with higher doses potentially increasing IOP.[27] Given the limitations and potential for adverse effects on optic nerve blood flow, cannabis is not considered a primary treatment option for glaucoma. Side effects can include psychotropic effects (euphoria/dysphoria, memory disruption, cognitive impairments), postural hypotension, tachycardia, palpitations, and altered mental status.[19]

Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS)

Inflammatory Bowel Disease (IBD) encompasses chronic inflammatory conditions of the gastrointestinal (GI) tract, primarily Crohn's disease (CD) and ulcerative colitis (UC).[4] Irritable Bowel Syndrome (IBS) is a functional GI disorder often grouped with IBD in cannabis research.[4] Patients with these conditions frequently experience debilitating symptoms such as abdominal pain, cramping, nausea, diarrhea, and weight loss.[30]

The endocannabinoid system, when activated, plays a role in modulating GI function by reducing gut motility, intestinal secretion, and epithelial permeability.[30] It also influences inflammatory leukocyte recruitment and immune modulation through cannabinoid receptors present in the enteric nervous and immune systems.[30] Preclinical studies in animal models have shown cannabis to exert strong anti-motility and anti-inflammatory effects on the gut.[30] Both THC and CBD have demonstrated the ability to decrease inflammation.[31]

Epidemiological data suggest a possible role for cannabinoids in the *symptomatic treatment* of IBD.[31] Patients frequently report substantial therapeutic effects, including relief from abdominal pain, joint pain, cramping, diarrhea, poor appetite, weight loss,

and nausea.[31] A small placebo-controlled study for active Crohn's disease showed a clinical response (defined as a decrease in CDAI by >100 points) in 10 out of 11 cannabis-treated patients compared to 4 out of 10 in the placebo group (P=0.028).[30] Cannabis use has also been associated with improved quality of life, increased patient weight and BMI, and improved clinical disease activity index in CD patients.[31]

However, a critical observation arises from one study which suggested that while cannabis provides symptomatic relief in IBD patients, it is "associated with worse disease prognosis in patients with Crohn's disease".[30] This profound divergence highlights a crucial distinction between symptom management and actual disease modification. It implies that while patients may experience symptomatic improvement and feel better, the underlying inflammatory disease may not be improving, or could even be worsening, with cannabis use. Such a scenario could lead to a false sense of security, potentially delaying or leading to inadequate conventional treatment, and ultimately impacting long-term disease outcomes.

Due to small sample sizes and short follow-up durations in many studies, it remains challenging to demonstrate clear, consistent benefits of cannabis in IBD.[30] Both THC and CBD have shown anti-inflammatory effects [31], and THC is primarily implicated in symptomatic relief.[30] Cannabis provides symptomatic relief but is not a cure for IBD or IBS. Adverse effects are typically mild to moderate and include dry mouth, drowsiness, sleepiness, a feeling of being "high," nausea, anxiety, and paranoia.[30] Patients using higher doses for symptom control may face an increased risk of cannabis dependency.[30] Long-term use has also been associated with altered brain development, memory and cognitive impairments, and altered judgment.[30]

Post-Traumatic Stress Disorder (PTSD)

Post-Traumatic Stress Disorder (PTSD) is a mental health condition that can develop after experiencing or witnessing a terrifying event.[28] It is characterized by intrusive thoughts, nightmares, avoidance behaviors, negative changes in thinking and mood, and alterations in physical and emotional reactions.[28]

THC activates CB1 receptors, modulating neuronal functions by reducing presynaptic neurotransmitter release (e.g., glutamate, GABA, and acetylcholine), inducing synaptic plasticity, and adjusting energy metabolism.[13] This interaction can influence the extinction of aversive memories and the accompanying anxious thoughts and

behaviors.[32] CBD is also noted to exhibit promising therapeutic properties.[13]

Evidence regarding cannabis effectiveness for PTSD primarily stems from low-quality, observational studies with a high risk of bias and often lacking comparators.[33] These studies suggest that cannabis use is associated with a reduction in overall PTSD symptoms and an improved quality of life.[33] A mild euphoria or sense of well-being induced by cannabinoids could potentially play a therapeutic role for patients experiencing the despair associated with terminal or chronic illnesses.[32]

However, a critical observation reveals significant risks: high doses of THC can *increase anxiety* and trigger *schizophrenia-like symptoms*.[13] Furthermore, daily use of cannabis products with high THC content is associated with an increased risk of developing psychotic disorders, including schizophrenia.[13] Some patients in studies have even experienced a

worsening of PTSD symptoms.[33] This highlights a narrow therapeutic window and significant risks, particularly with high-THC products, making careful patient selection and monitoring absolutely crucial. The complex and potentially dangerous interplay between cannabinoid composition and individual psychiatric vulnerability means that the therapeutic application for PTSD is highly nuanced, requiring careful consideration of cannabinoid profiles, dosing, and a patient's psychiatric history.

Both THC and CBD exhibit promising therapeutic properties for PTSD.[13] THC's effects on memory and anxiety are dose-dependent and can be biphasic, meaning low doses may have one effect while high doses have the opposite.[13] Cannabis provides symptomatic relief for PTSD but is not a cure. Side effects include dry mouth, headaches, psychoactive effects (agitation, euphoria), cognitive difficulties (slowed mentation, memory lapses, poor concentration), dizziness, confusion, disorientation, increased heart rate, sweating, anxiety, weakness, impaired judgment, and psychosis.[13] Significant side effects are also associated with chronic use of high-dose CBD.[13]

Tourette Syndrome

Gilles de la Tourette Syndrome (GTS) is a developmental neuropsychiatric disorder characterized by the presence of chronic motor and phonic tics.[28] Patients with Tourette Syndrome may also experience associated symptoms such as anxiety and

obsessive-compulsive disorder (OCD).[35]

Cannabinoids are believed to modulate neurotransmitter systems involved in the generation of tics, although the precise mechanisms are still being elucidated.

Preliminary evidence suggests a potential benefit from cannabis products containing Δ9-THC, and the coadministration of CBD appears to improve the side-effect profile and overall safety.[35] A double-blind, crossover trial involving 22 participants with severe Tourette Syndrome found a significant reduction in total tic score on the Yale Global Tic Severity Scale (YGTSS) when treated with an oral oil containing 5 mg/ml of both THC and CBD, compared to placebo.[35] This treatment may also reduce impairment due to tics, anxiety, and obsessive-compulsive symptoms.[35]

Two earlier trials comparing Δ9-THC (either as monotherapy or adjuvant therapy) with placebo also reported a positive effect on tic reduction.[34] However, the improvements in tic frequency and severity were generally small and only detected by some outcome measures.[34] These studies had major limitations, including relatively small sample sizes (a total of 28 different patients across both trials) and a large number of multiple comparisons, which can impact the reliability of the findings.[34] Therefore, longer trials with larger numbers of patients are necessary to establish the long-term efficacy and safety of cannabinoids in treating Tourette Syndrome symptoms.[34]

THC is primarily associated with tic reduction.[34] CBD coadministration plays a role in improving the side-effect profile and safety of the treatment.[35] Cannabis provides symptomatic relief for tics and associated symptoms; it is not a cure for Tourette Syndrome. The most common adverse effect observed in the active treatment period of one trial was cognitive difficulties, including slowed mentation, memory lapses, and poor concentration.[35] Headache was a common adverse effect in the placebo group.[35] General side effects of Δ9-THC can include dizziness and dry mouth.[34]

Other Conditions with Emerging or Limited Evidence

Medical cannabis is being explored for a broader range of conditions, with varying levels of scientific evidence supporting its use. For many of these, the evidence is still emerging, limited, or inconsistent, and further rigorous research is required.

- **Alzheimer's Disease:** Listed as a qualifying condition in Minnesota and by Cleveland Clinic.[4] Dronabinol has been noted to help manage agitation in severe

dementia.[4] Research is ongoing into its potential role.[1]

- **Amyotrophic Lateral Sclerosis (ALS):** Recognized as a qualifying condition in Minnesota, New Jersey, and by Cleveland Clinic.[4]
- **Anxiety:** Listed as a qualifying condition in New Jersey.[29] CBD may hold therapeutic potential for anxiety.[16] However, it is crucial to note that high doses of THC can paradoxically increase anxiety.[13]
- **Autism Spectrum Disorder:** Listed as a qualifying condition in Minnesota.[28]
- **Chronic Motor or Vocal Tic Disorder:** Listed as a qualifying condition in Minnesota.[28]
- **Dysmenorrhea:** Listed as a qualifying condition in New Jersey.[29]
- **Fibromyalgia:** Listed as a qualifying condition by Cleveland Clinic.[4]
- **Hepatitis C:** Listed as a qualifying condition by Cleveland Clinic.[4]
- **HIV/AIDS:** Listed as a qualifying condition in Minnesota, New Jersey, and by Cleveland Clinic.[4] Dronabinol is FDA-approved for appetite loss and weight loss in HIV/AIDS.[4] However, as of 2013, evidence for both the efficacy and safety of cannabis and cannabinoids in treating HIV/AIDS patients or for anorexia associated with AIDS was lacking, with existing studies often suffering from bias, small sample sizes, and an absence of long-term data.[16]
- **Huntington's Disease:** Listed as a qualifying condition by Cleveland Clinic.[4]
- **Insomnia:** A review up to 2018 indicates that CBD may have therapeutic potential for insomnia.[16] Conversely, research analyzing data from the National Health and Nutrition Examination Survey (NHANES) did not find significant differences in overall sleep duration between cannabis users and non-users.[16] THC can induce sleepiness or sedation [4], and improved sleep has been noted in advanced cancer patients receiving high-dose THC.[14]
- **Irritable Bowel Syndrome (IBS):** Listed as a qualifying condition in Minnesota and by Cleveland Clinic.[4] Research often groups IBS with IBD for cannabis studies.
- **Migraine:** Listed as a qualifying condition in New Jersey.[29] One study indicated that abortive or preventive treatment with cannabis was associated with a reduction in migraine frequency from 10.4 to 4.6 migraines per month.[11] However, results for other headache disorders have been mixed.[11]
- **Muscular Dystrophy:** Listed as a qualifying condition in New Jersey.[29]
- **Obsessive-Compulsive Disorder (OCD):** Listed as a qualifying condition in Minnesota.[28] Some weak evidence suggests that cannabinoid medication may have an effect on obsessive-compulsive behavior.[34]
- **Obstructive Sleep Apnea:** Listed as a qualifying condition in Minnesota.[28]
- **Opioid Use Disorder:** Listed as a qualifying condition in New Jersey.[29] Some epidemiological studies suggest a possible reduction in reliance on opioid pharmacotherapy for pain as a result of increased medical cannabis regimens,

which could potentially lead to fewer fatal opioid overdoses.[21]

- **Parkinson's Disease:** Listed as a qualifying condition by Cleveland Clinic.[4] Neurological disorders, including Parkinson's, are an area of ongoing research for cannabinoids.[1]
- **Sickle Cell Disease/Anemia:** Listed as a qualifying condition in Minnesota and by Cleveland Clinic.[4] However, a significant observation is that long-term marijuana use has been associated with *more frequent pain crises* in sickle cell patients.[15] This represents a profound contradiction, indicating a potential disconnect between state-level medical cannabis approvals, which may be based on anecdotal reports or limited initial data, and emerging scientific findings. This discrepancy highlights a critical safety concern and underscores the urgent need for more rigorous, condition-specific research to ensure patient safety and efficacy.
- **Skin Disorders:** Initial clinical reports suggest cannabinoids may have potential benefits for skin disorders.[2] An ointment containing CBD and CBG has shown effectiveness in treating symptoms of eczema.[7]
- **Spinal Cord Injury or Disease:** Listed as a qualifying condition by Cleveland Clinic.[4]
- **Terminal Illness (Palliative Care):** Listed as a qualifying condition in Minnesota, New Jersey, and by Cleveland Clinic.[4] Symptom management is a key goal of palliative cancer care.[14] Well-documented and evidence-based indications include severe pain, muscle spasm, intractable nausea, and cachexia.[32] Studies have shown significant improvement in cancer-related or anti-cancer treatment-related symptoms such as nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sleep disorders, itching, and pain.[32] Patients have reported improvements in general well-being, appetite, and nausea.[32] A reduction in opioid pain medication dose has been observed in some patients [32], and less reliance on opioid pharmacotherapy may contribute to fewer fatal opioid overdoses.[21] A mild euphoria or sense of well-being from cannabinoids can play a therapeutic role for patients facing the despair of a terminal illness.[32] There is growing evidence suggesting cannabinoid therapies might have disease-modifying effects in cancer and neurological disorders, with preclinical evidence indicating they might enhance the antitumour activity of conventional chemotherapeutic agents.[32] A strong consensus supports cannabis as a potential anticarcinogenic agent.[6] THC at higher doses (15-20mg) provided better pain relief but with more adverse effects.[14] THC:CBD extract was efficacious for pain relief in advanced cancer pain not fully relieved with strong opioids.[14] Primarily, cannabis serves for symptomatic management and quality of life improvement in terminal illness, not as a cure. Side effects include mood changes, somnolence,

and visual distortions or hallucinations.[14]

- **Chronic Traumatic Encephalopathy (CTE):** Listed as a qualifying condition by Cleveland Clinic.[4]
- **Urologic Symptoms:** The endocannabinoid system influences the urologic system, and cannabis products are being investigated for their potential use in treating lower urinary tract symptoms and other urologic symptoms.[10]

Table 2: Summary of Conditions and Cannabis Efficacy (Evidence Level)

Condition/Disease	Primary Symptom(s) Addressed	Key Cannabinoid(s) Involved	Level of Scientific Evidence	Treatment or Cure?	Key Caveats/Limitations
Chronic Pain	Pain (neuropathic, chronic)	THC, CBD (combination)	Conclusive/Substantial (general), Inconsistent (specific types)	Treatment/Symptomatic Relief	Efficacy dependent on pain type, administration; inconsistent for cancer pain; potential placebo effect; long-term use risk of CUD.
CINV	Nausea, Vomiting	THC, CBD, CBDA	Conclusive/Substantial (oral cannabinoids)	Treatment/Symptomatic Relief	More side effects than conventional antiemetics; CBD has narrow effective window; THC can be sedating.
Epilepsy (LGS, DS)	Seizures	CBD (purified)	Conclusive/Substantial (for LGS, DS)	Treatment/Symptomatic Relief	FDA-approved for specific rare epilepsies; not clear for

					general seizures; adjunct therapy only; drug interactions (CYP enzymes).
Multiple Sclerosis	Spasticity, Muscle Stiffness, Pain	THC, CBD (1:1 ratio for Sativex)	Substantial/Emerging	Treatment/Symptomatic Relief	Add-on therapy; common side effects like dizziness, dry mouth.
Appetite Loss/Cachexia	Appetite loss, Weight loss	THC, CBD (combination)	FDA-approved (Dronabinol for HIV/AIDS); Inconsistent (general cachexia)	Treatment/Symptomatic Relief	No statistically significant change in appetite for general cachexia; gain mostly fat mass; potential for immune modulation.
Glaucoma	Intraocular Pressure (IOP)	THC, CBD	Limited/Inconsistent	Treatment/Symptomatic Relief (temporary)	Short-lived effect; potential to decrease optic nerve blood flow (risk for vision loss); tolerance develops.
IBD/IBS	Abdominal pain, Nausea, Diarrhea, Cramping	THC, CBD	Emerging/Limited	Treatment/Symptomatic Relief	Small study sizes; may be associated with *worse prognosis* in

					Crohn's disease; risk of dependency.
PTSD	PTSD symptoms, QOL	THC, CBD	Limited/Observational	Treatment/Symptomatic Relief	High THC doses can *increase anxiety* and psychosis risk; worsening of symptoms reported; narrow therapeutic window.
Tourette Syndrome	Tics, Anxiety, OCD symptoms	THC, CBD	Preliminary/Limited	Treatment/Symptomatic Relief	Small study sizes; cognitive side effects (slowed mentation, memory lapses).
Sickle Cell Disease	Pain crises	N/A	Contradictory	N/A (Potential Harm)	Long-term use associated with *more frequent pain crises*.
Terminal Illness (Palliative Care)	Pain, Nausea, Vomiting, Mood, Appetite, Sleep	THC, CBD	Emerging/Promising	Treatment/Symptomatic Relief	Focus on QOL; potential antineoplastic effects but not a cure.

IV. General Considerations for Medical Cannabis Use

Dosage and Administration Guidelines ("Start Low, Go Slow" Principle)

Determining the appropriate dosage for medical cannabis is complex due to numerous influencing factors, including an individual's genetics, age, sex, the specific cannabis strain (Indica, Sativa, or hybrid), the chosen delivery method, and individual metabolism.[4] The guiding principle for medical cannabis use, particularly for cannabis-naive individuals or when using THC-containing products, is "start low and go slow".[22] This approach aims to minimize adverse events and allow for the gradual development of tolerance.

The wide variability in dosage recommendations across different administration methods and cannabinoid ratios, coupled with the pervasive "start low, go slow" principle, highlights a significant absence of standardized, universally accepted dosing protocols for medical cannabis. This implies that effective and safe use heavily relies on individualized titration and meticulous patient self-monitoring, posing considerable challenges for both healthcare providers and patients in achieving optimal therapeutic outcomes while minimizing adverse effects. Unlike conventional pharmaceuticals where precise dosage instructions are provided, medical cannabis often requires a trial-and-error approach, which can be inefficient and potentially lead to suboptimal or adverse experiences.

Administration Protocols and General Guidelines:

- **Oral Dosing (Edibles, Tinctures, Capsules):** These methods result in a slower absorption of the compounds, leading to a delayed onset (60-180 minutes) but a more prolonged duration of effect (6-8 hours).[22] A recommended starting dose is 1 mg to 2.5 mg THC-equivalent at bedtime, with gradual increases of 1-2.5 mg every two days until the desired effect is achieved or side effects become limiting.[22] For daytime use, 1-2.5 mg THC-equivalent twice daily, increasing as tolerated up to 15 mg THC-equivalent per 24 hours, is suggested.[22] For products with a high CBD to THC ratio (approximately 20:1), patients over 110 pounds can begin with 25 mg of CBD twice daily, increasing by 25 mg every one to two weeks up to a maximum of 600 mg daily.[23] Doses exceeding 20-30 mg THC per day may increase the likelihood of adverse events.[22]
- **Inhalation (Vaporizer, Vape Pens, Smoking):** Inhaled cannabis offers a rapid onset of action (5-10 minutes) because the lungs absorb compounds almost instantly, providing immediate but shorter-lived relief (2-4 hours).[22] This method is

advantageous for acute or episodic symptoms and allows for easier rapid titration.[22] A starting dose involves one full inhalation (5-second draw, 10-second hold), followed by a 15-minute waiting period before adding another inhalation every 15-30 minutes until symptom control is achieved or side effects limit use.[22] Dosing intervals typically range from every 2-4 hours.[22] Most patients using a vaporizer device consume 1-3 grams of herbal cannabis per day, with dose escalation generally not observed over time.[22] Vape pens are often used for acute relief or breakthrough symptoms.[22]

- **Sublingual (Oil, Extract, Tincture):** This method provides an onset of 15-45 minutes and a duration of 6-8 hours.[22] Dosing recommendations are similar to oral methods for CBD-predominant products.[22]
- **Topical (Oil, Cream/Ointment):** Topical products offer localized relief without systemic effects, with an onset of approximately an hour.[22]

Potential Side Effects and Adverse Reactions

The use of medical cannabis is associated with a range of potential side effects, varying in severity from mild and transient to serious psychiatric and cardiovascular risks. This broad spectrum of effects underscores the non-trivial nature of medical cannabis use. The dose-dependent and often biphasic effects of THC—where low doses may induce euphoria, but higher doses can lead to anxiety or psychosis—highlight the critical importance of careful titration and vigilant patient monitoring, particularly for vulnerable populations.

Common Short-Term Effects: These include headaches, dry mouth and eyes, lightheadedness, dizziness, drowsiness, fatigue, nausea and vomiting (though paradoxical nausea and vomiting, known as cannabinoid hyperemesis syndrome, can occur with long-term use), disorientation, confusion, euphoria, mood changes, increased heart rate, increased appetite, impaired memory, issues with thinking and problem-solving, impaired coordination, and slowed reaction time.[4]

More Serious Effects:

- **Psychosis:** There is an increased risk of psychosis in individuals with schizophrenia, especially with frequent use of high-potency marijuana (high THC levels).[4] Acute reversible psychotic reactions have also been documented.[15]
- **Anxiety/Panic Attacks:** Cannabis use can worsen manic symptoms in individuals

with bipolar disorder and increase anxiety, particularly with higher THC doses.[5] Panic attacks are among the most common emergencies resulting from marijuana ingestion.[15]

- **Respiratory Issues:** Long-term smoking of cannabis can exacerbate respiratory conditions, including bullous emphysema, and lead to increased wheezing, coughing, and phlegm production.[5]
- **Cardiovascular Effects:** These include increased heart rate, high blood pressure, postural hypotension, tachycardia, and potential cardiotoxicity.[5]
- **Cannabinoid Hyperemesis Syndrome (CHS):** Paradoxically, long-term cannabis use can lead to a condition characterized by recurrent bouts of severe nausea and vomiting.[16]
- **Dependence and Withdrawal:** There is a risk of developing cannabis use disorder (CUD), with a higher risk observed in youth users.[1]
- **Liver Enzyme Elevation:** The use of Epidiolex, especially when combined with valproate, can lead to elevated liver enzymes.[8]

The pattern of these risks indicates that they are not uniform but are amplified by specific factors: high THC content, chronic use, younger age, and pre-existing psychiatric vulnerabilities. This moves beyond a simple list of side effects to a risk stratification model, emphasizing the need for thorough patient assessment, comprehensive education, and potentially avoiding cannabis in high-risk groups.

Drug Interactions

Medical cannabis is a pharmacologically active agent that can significantly interact with various medications, influencing their blood levels or producing additive effects.[4] The extensive list of documented drug interactions, particularly those mediated by cytochrome P450 enzyme inhibition and additive central nervous system (CNS) or cardiovascular effects, indicates that medical cannabis is not a benign additive to existing pharmacotherapy. This complexity demands a comprehensive medication review by healthcare providers, treating cannabis with the same rigor as any prescription drug, to prevent potentially dangerous drug-drug interactions, especially in patients with polypharmacy or those on critical medications with narrow therapeutic indices.

Increased Blood Levels of Medications: CBD and/or marijuana/THC can increase

the blood concentrations of several medications, including:

- Clobazam (an antiseizure medication and benzodiazepine).[4]
- Warfarin (an anticoagulant).[4]
- Diclofenac (a type of NSAID).[4]
- Certain antipsychotic medications and antidepressants.[4]
- Substrates of CYP2B6, UGT1A9, UGT2B7, CYP2C8, and CYP2C9 enzymes. CBD is a potent inhibitor of CYP2C19 and CYP3A4, which are crucial for metabolizing many drugs.[15]

Decreased Brain Concentrations: THC can decrease brain concentrations of risperidone, an antipsychotic medication.[4]

Additive Effects:

- **CNS Depressants:** Concurrent use of cannabis with barbiturates, benzodiazepines, lithium, buspirone, antihistamines, muscle relaxants, anesthesia, or other CNS depressants can result in significant CNS depression.[5] It is advised to avoid marijuana use two weeks prior to planned surgery.[5]
- **Cardiovascular Drugs:** When cannabis is used concurrently with drugs that have comparable cardiovascular effects (e.g., hypotension, hypertension, and tachycardia), there is a potential for additive cardiac effects, including syncope.[15]
- **Sympathomimetic Drugs:** Concurrent use with amphetamines, cocaine, and other sympathomimetic drugs might lead to additive hypertension, tachycardia, and potential cardiotoxicity.[15]
- **Tricyclic Antidepressants:** Medications such as amitriptyline, amoxapine, and desipramine, when used with cannabis, might induce additive tachycardia, hypertension, and drowsiness.[15]

Reduced Effectiveness: Marijuana might reduce the effectiveness of protease inhibitors, which are antiviral drugs.[5]

Contraindications and Precautions

The comprehensive and specific list of contraindications and precautions for medical cannabis, particularly concerning neurological development in youth, fetal and infant health, pre-existing psychiatric conditions, and organ dysfunction, profoundly reframes it from a benign herbal remedy to a potent pharmacological agent with

significant, targeted risks. This necessitates a highly individualized and medically supervised approach, emphasizing rigorous patient screening and risk assessment over broad accessibility, to prevent severe and irreversible adverse outcomes in vulnerable populations.

- **Youth (under 25):** The human brain continues to develop until approximately age 25. Cannabis use in early teenage years can alter brain structure and lead to lasting problems with attention span, memory, and other mental functions.[36] There is a higher risk of dependency and developing psychosis or schizophrenia in this age group.[36] Cannabis is generally not recommended for patients aged 8 and younger.[15]
- **Pregnancy and Breastfeeding:** Cannabis use is not recommended during pregnancy due to the potential for fetal harm.[15] Heavy cannabis use by pregnant individuals has been linked to a greater risk of premature birth, lower birth weight, lower alertness, and slower growth in babies.[36] THC can pass into breastmilk and enter the baby's brain and fat cells, where it may remain for weeks, potentially affecting the baby's sleep and later school performance.[36]
- **Men who want to be dads:** Cannabis has been shown to reduce sperm count, mobility, and concentration, and may increase abnormal sperm structure, making conception more challenging.[36]
- **Personal or Family History of Psychosis, Schizophrenia, or Bipolar Disorder:** Heavy cannabis use, especially when there is a family history of mental illness, may trigger a psychotic reaction and regular use can increase the risk of longer-lasting psychotic episodes.[36] It can also worsen manic symptoms in individuals with bipolar disorder.[5]
- **Personal or Family History of Depression:** Cannabis use may worsen the symptoms of depression.[5]
- **Severe Liver, Kidney, Heart, or Lung Disease:** Frequent cannabis use can negatively affect these vital organs.[36] Specific medical contraindications include cardiovascular disease, arrhythmias, poorly controlled hypertension, and severe heart failure.[15] Hepatotoxicity has been observed with CBD, particularly when used concomitantly with valproate.[15]
- **History of Substance Use Disorder:** Marijuana is classified as a Schedule I substance by the U.S. Drug Enforcement Administration (DEA) due to its high potential for addiction.[4] Long-term recreational use can develop into cannabis use disorder (CUD).[1]
- **Planned Surgery:** Due to its central nervous system (CNS) depressant effects and the potential for additive effects with anesthesia, marijuana use should be avoided two weeks prior to any planned surgery.[5]

- **Hypersensitivity/Allergy:** Dronabinol is contraindicated in individuals with hypersensitivity to the drug, cannabinoids, propylene glycol, or peppermint oil.[15]

Importance of Medical Supervision and Individualized Treatment Plans

The inherent variability in individual patient responses, the heterogeneous nature of cannabis preparations, and the evolving scientific evidence collectively underscore the critical necessity for medical cannabis use to be managed under stringent medical supervision with highly individualized treatment plans. This paradigm shifts the responsibility from self-medication to a collaborative clinical approach, where healthcare providers, armed with evolving research, guide patients through precise titration and ongoing monitoring to optimize therapeutic outcomes while mitigating complex risks.

In states where medical cannabis is legal, healthcare providers may certify or confirm that a person has a medical condition with symptoms that cannabis may treat or alleviate, but they cannot directly prescribe the marijuana plant.[4] Some states require an established practitioner-patient relationship, such as one that has existed for at least one year or involves at least four visits for the debilitating medical condition.[29] The inconclusiveness often observed in cannabis research, stemming from the heterogeneous nature of studied populations, diverse cannabis preparations and dosages, and uncontrolled settings, further emphasizes the need for highly individualized approaches in clinical practice.[3]

Table 3: General Side Effects, Drug Interactions, and Contraindications of Medical Cannabis

Category	Details
Common Side Effects	Headaches, dry mouth and eyes, lightheadedness, dizziness, drowsiness, fatigue, nausea, vomiting (can be paradoxical with long-term use), disorientation, confusion, euphoria, mood changes, increased heart rate, increased appetite, impaired memory, issues with thinking and problem-solving, impaired coordination, slowed reaction time.

Serious Side Effects/Risks	Psychosis (increased risk, especially with high-THC in vulnerable individuals), increased anxiety/panic attacks (dose-dependent), worsening of pre-existing mental health conditions (e.g., bipolar, depression), respiratory issues (long-term smoking), cardiovascular effects (tachycardia, hypotension, hypertension, cardiotoxicity), Cannabinoid Hyperemesis Syndrome (CHS), Cannabis Use Disorder (CUD), liver enzyme elevation (especially with Epidiolex + valproate).
Key Drug Interactions	**Increased Blood Levels of:** Clobazam, Warfarin, Diclofenac, certain antipsychotics/antidepressants, and drugs metabolized by CYP2B6, UGT1A9, UGT2B7, CYP2C8, CYP2C9 (due to CBD's inhibition of CYP2C19, 3A4, 2D6). **Decreased Brain Concentrations of:** Risperidone. **Additive Effects with:** CNS depressants (barbiturates, benzodiazepines, anesthesia), cardiovascular drugs (hypotension, hypertension, tachycardia), sympathomimetic drugs (amphetamines, cocaine), tricyclic antidepressants. **Reduced Effectiveness of:** Protease inhibitors.
Contraindications/Precautions	**Absolute:** Youth (under 25 due to brain development), Pregnancy/Breastfeeding (fetal/infant harm), Personal/Family history of psychosis/schizophrenia/bipolar disorder, Severe liver/kidney/heart/lung disease, Hypersensitivity to specific cannabinoids/components. **Relative:** Men desiring conception (sperm effects), History of depression (may worsen), History of substance use disorder (addiction potential), Planned surgery (avoid 2 weeks prior).

V. Conclusion

Medical cannabis presents an evolving landscape of therapeutic potential, offering established or emerging benefits for a range of conditions, primarily focused on

symptomatic relief and improving quality of life. Its effects are mediated through the complex interactions of various cannabinoids, notably THC and CBD, with the widespread endocannabinoid system. Conditions such as chronic pain, chemotherapy-induced nausea and vomiting (CINV), specific forms of epilepsy (Lennox-Gastaut and Dravet syndromes), multiple sclerosis-related spasticity, and appetite loss in HIV/AIDS have demonstrated varying degrees of responsiveness to cannabis-based interventions. The use of cannabis in palliative care for terminal illness also shows promise in managing a spectrum of distressing symptoms and enhancing overall well-being.

However, it is crucial to consistently reiterate that cannabis serves as a *treatment* for symptoms or conditions, offering relief or management, and is *not a cure* for any disease. While there is a growing consensus on its therapeutic benefits, particularly as a palliative adjunct in cancer care, and emerging evidence for potential anticarcinogenic effects, these do not equate to curative claims.

The application of medical cannabis is associated with significant limitations and complexities. These include inconsistent evidence for certain conditions, the potential for serious side effects (particularly psychiatric and cardiovascular effects), numerous documented drug interactions, and clear contraindications for vulnerable populations such as youth, pregnant or breastfeeding individuals, and those with a history of psychosis or severe organ disease. The cannabis plant itself remains unapproved by the FDA for medical use, although specific purified cannabinoid analogs have received approval following rigorous clinical trials.

The persistent demand for "further randomized controlled trials" across numerous conditions, despite an acknowledged "strong and growing consensus" on cannabis's therapeutic benefits in areas like palliative care, reveals a fundamental tension between accelerating public and medical interest and the rigorous, slow pace of conventional pharmaceutical validation. This indicates that while real-world utility and symptomatic relief are increasingly recognized, the scientific community still lacks the high-quality, standardized evidence necessary to fully integrate cannabis into mainstream pharmacotherapy. This ongoing challenge is compounded by the complex nature of the cannabis plant, with its varied chemical profiles, and the regulatory hurdles that impede large-scale, standardized research.

Future research must prioritize rigorous randomized controlled trials (RCTs) with larger sample sizes, longer durations, and standardized cannabis preparations and dosages to provide definitive recommendations. Further investigation into the "entourage effect"—the synergistic interaction of multiple cannabinoids and

terpenes—and the identification of optimal THC:CBD ratios for specific conditions are essential. Continued elucidation of the biological mechanisms of action for various cannabinoids will also be critical. The evolving landscape of cannabis policies and public perceptions necessitates ongoing public health initiatives and comprehensive education for both patients and healthcare providers. Healthcare professionals must engage in thorough risk-benefit discussions with patients, meticulously considering individual factors, comorbidities, and potential drug interactions to ensure safe and effective use of medical cannabis.

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