A Narrative Review

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# Medical Cannabis for Chronic Pain: A Narrative Review of the Evidence, Challenges, and Future Directions.

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## Abstract

### Introduction

Chronic pain has been amongst the leading health issues globally, often treated with opioids carrying a significant level of risk. Medical Cannabis, in its forms like THC and CBD, has been used as an alternative, acting by endocannabinoid system interaction for pain management and inflammation [1]. This review shines light on recent evidence based research on the safety, efficacy and the potential of MC for chronic pain modulation. The evidence for potential benefits remains inconsistent despite several studies reporting benefits like pain reduction in fibromyalgia, MS-associated neuropathic pain, opioid-sparing effects and outcomes like improved sleep pattern and quality of life, reported by the patients [2].A significant variation of efficacy is found, by pain condition and cannabis formulation, in high quality RCTs yielding contradictory or inconsistent results. Some of the challenges include lack of guidelines for dosing and product standardization, psychiatric and cognitive adverse effects, drug interactions, and regulatory constraints. All in all, medical cannabis promises potential, but with practical challenges and significant gaps in evidence, it presents a clinical conundrum [3,4]. More rigorous research is required urgently with individualized application, policy harmonization and clearly defined guidelines which are evidence based[5].Chronic pain remains a significant health crisis globally, affecting emotional, physical, and socio-economic well-being on a remarkable scale[6].Other contemporary analgesic therapies like opioids sometimes fail to provide optimal response to patients and also pose various risks including tolerance, drug dependence, and unwanted side effects[7]. As a result, a great amount of interest has been emerging for alternative treatment regimens like medical cannabis, focusing on its potential as a safer and better option for the management of persistent pain [8].

**Keywords:** Medical Cannabis, THC, CBD, Cannabinoids, Pain Management, Chronic Pain

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## Introduction

Chronic pain remains a significant health crisis globally, affecting emotional, physical, and socio-economic well-being on a remarkable scale [9, 11]. Other contemporary analgesic therapies like opioids sometimes fail to provide optimal response to patients and also pose various risks including tolerance, drug dependence, and unwanted side effects [6, 18]. As a result, a great amount of interest has been emerging for alternative treatment regimens like medical cannabis, focusing on its potential as a safer and better option for the management of persistent pain [2, 4, 7].Medical cannabis, which encompasses a wide range of compounds including cannabidiol [CBD] and THC [delta-9-tetrahydrocannabinol] [2, 8, 26], has been in the limelight of a renewed clinical attention, especially for conditions that are complex and complicated to treat like symptoms refractory to standard care or neuropathic pain [1, 2]. However, it has been a very taxing and slow process to integrate medical cannabis into the world of mainstream medicine. This is mostly because of a major lacking in terms of high-quality research and strong clinical evidence, largely inconsistent dosing approaches, political stances, and wide differences in the manufacture of these products including them

composition [3, 6]. Although the science keeps on evolving, the evidence remains heterogeneous and often contradictory, made worse by clinical decision-making [2, 3]. The potential for cannabinoids as analgesics is primarily through cannabinoid-2 and cannabinoid-1 receptors interacting with the body's endocannabinoid system, a modulator of pain, inflammation, and mood [2, 8, 26].Recent studies exemplify this complexity. Recent evidence highlights this, while a retrospective case series of patients with fibromyalgia consulted Maza et al. showed a significant improvement in symptoms of patients unresponsive to normal therapy [2], a randomized controlled trial [RCT] carried out using standardized THCA: CBDA capsules found no additional benefit compared to placebo for peripheral neuropathic pain [3]. Additionally, attempts to utilize the cannabinoid-opioid synergetic effects have shown mixed results when tested, one trial by Camacho et al. showed that adding THC to hydromorphone did not improve pain but did increase adverse events [18]. Interpreting the available data is thus complicated by variations in cannabis formulations [21], dosing strategies, patient populations [6, 29], and overall study quality [6, 7].

## Relevance of Medical Cannabis

Despite evidentiary challenges, growing clinical and institutional interest is undeniable, reflected by increasing trial registrations [17] and research spurred by legislative shifts [18]. Evidence hints at potential utility in specific niches. Reviews and observational data suggest possible associations between cannabis use and reduced opioid consumption or improved pain scores in cancer pain [7], with formulations like nabiximols showing promise in opioid-refractory cases [28]. Real-world data also support potential benefits in treatment-resistant fibromyalgia [2], and cohort studies indicate mild-to-moderate improvements in mixed chronic pain populations, potentially predicted by factors like prior opioid use [16]. Technological advancements like selective-dose inhalers [14] or formulations balancing THC: CBD ratios [29] aim to improve consistency and tolerability. Research continues across diverse applications, from low-dose oral CBD [13] and transdermal CBD [17] to formulations for adolescent migraine [21]. However, the promise is tempered by inconsistent efficacy. Modest or non-significant results have been reported in rheumatoid arthritis [5], sickle cell disease pain [9], MS/SCI-related pain [28], HIV-neuropathy [20], and experimental pain models [19]. Meta-analyses often find small effect sizes with low certainty [22], leading organizations like the IASP to maintain cautious stances regarding recommendations [28].This variability underscores the complexity of applying cannabis clinically, demanding condition-specific evidence and personalized approaches considering pharmacokinetics [15] and patient factors like sex [16]. Safety remains a critical counterpoint, with documented risks including cognitive impairment, psychiatric effects, and dependency potential [10, 11], alongside concerns about unregulated OTC products [30] and high patient interest despite evidence gaps [11, 13].

## Objective

This Narrative Review aims to critically synthesize all available evidence to evaluate the clinical applicability of medical cannabis along with the safety and efficacy of its cannabinoid constituents in chronic pain management. It evaluates and integrates data from a wide spectrum of studies including RCTs, reviews, case studies, and observational data across a range of conditions like fibromyalgia, cancer pain, arthritis, multiple sclerosis, sickle cell disease etc., with different populations of patients which include older adults, adolescents, and people with end-stage chronic diseases, while considering the limitations in the methodological approaches and the obvious lack of high-quality research that needs to be conducted

## Thesis Statement

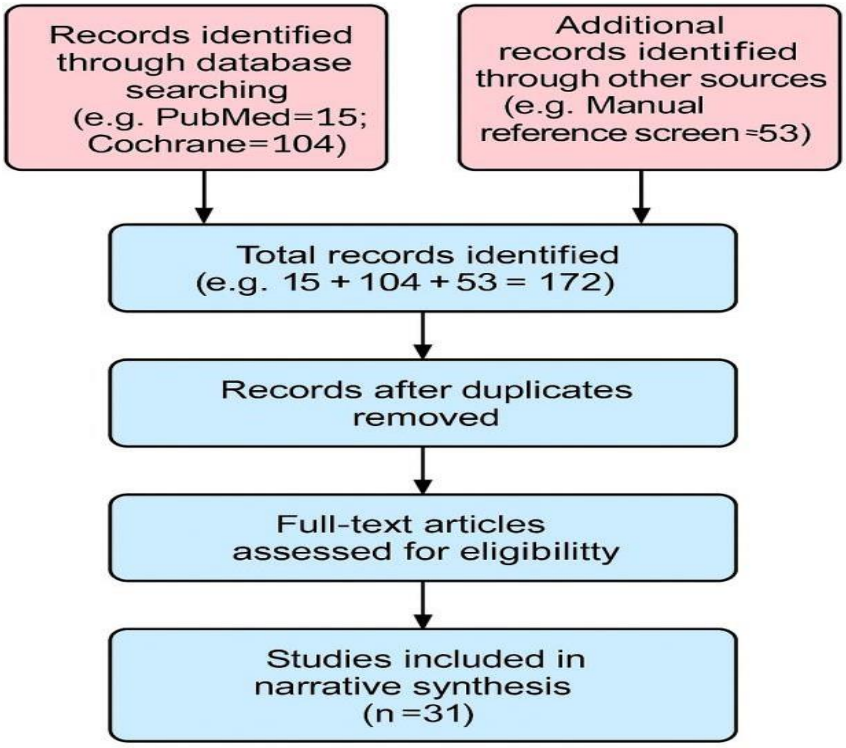
While medical cannabis research shows emerging promise as a complementary tool in chronic pain management, potentially reducing symptom burden in conditions like fibromyalgia [2] and aiding opioid reduction strategies [4, 6], its widespread adoption is hindered by inconsistent clinical outcomes across different pain types [3, 5, 20] and persistent safety concerns, including adverse psychotropic and systemic effects [10, 11, 22]. Clinical application necessitates a cautious approach grounded in condition-specific evidence and rigorous patient selection criteria [2, 3]. Discussing the future role of medical cannabis and resolving the current clinical uncertainties requires high-quality and more focused research to determine how much dosing is appropriate, if it's effective and if it interacts with other substances [18]. Such evidence is essential to support the development of clear and reliable clinical guidelines [5, 11, 21].

## Methodology

This narrative review synthesizes information regarding the role of medical cannabis in chronic pain management. A comprehensive literature search was conducted to inform the scope, exploring PubMed and

the Cochrane Library for studies published broadly between April 1, 2020, and March 31, 2025. The following representative search string indicates the concepts covered: ["medical cannabis" OR "cannabinoids" OR "CBD" OR "THC"] AND ["chronic pain" OR "neuropathic pain" OR "nociplastic pain" OR "fibromyalgia" OR "arthritis"] AND ["efficacy" OR "safety" OR "clinical trials" OR "adverse effects" OR "treatment outcome"]. Filters applied typically included free full text, English language, human studies, and age groups encompassing adolescents [13–18 years] and adults [19+ years], focusing on clinical trials, meta-analyses, and reviews while excluding preprints.This general search strategy yielded a wide range of potentially relevant literature. For the specific purpose of constructing *this* narrative review, the synthesis relied primarily on a curated set of sources provided by the user, supplemented by additional database searches and reference screening where necessary to ensure comprehensive coverage of the core topics. The sources included randomized controlled trials [RCTs] assessing efficacy and safety, systematic reviews and meta-analyses summarizing existing evidence, observational studies and case series providing real-world data, preclinical work informing mechanisms, feasibility studies, and trial protocols outlining future research.

**Figure 1:** *Flowchart of Study Selection Process*




The scope encompassed the use of various cannabis-based products [including THC, CBD, specific ratios like nabiximols, and whole-plant extracts] for different types of chronic pain [such as neuropathic pain, fibromyalgia, arthritis-related pain, cancer pain, and pain associated with conditions like MS, sickle cell disease, or end-stage kidney disease]. Key themes explored included efficacy, safety, cannabinoid mechanisms, historical context, clinical benefits [pain relief, opioid sparing, patient perspectives],clinical. dosing/standardization, interactions, regulatory barriers, ethics], comparisons with conventional treatments, and future research directions. Information was extracted thematically from the provided source materials and organized according to the predefined section headings of this review. The synthesis involved integrating findings across different study types and sources to build a narrative addressing the central question of whether medical cannabis represents a viable option or a clinical conundrum in chronic pain management.

Historical Context and Evolution of Cannabis Use Early UseHaving roots in the Middle East, India, and China, cannabis has a rich history of utilization for medicinal purposes going back centuries, mostly for its use in pain management, insomniac conditions and stomachache problems [4, 11, 15, 28]. Historically, its integration with early twentieth century medicine [6, 15] and with western medicine of the 19th-century [8] made a huge impact before the renaissance of the modern medicine [1, 12, 13]. Phytochemical identification [THC, CBD] occurred in the 20th century [10].

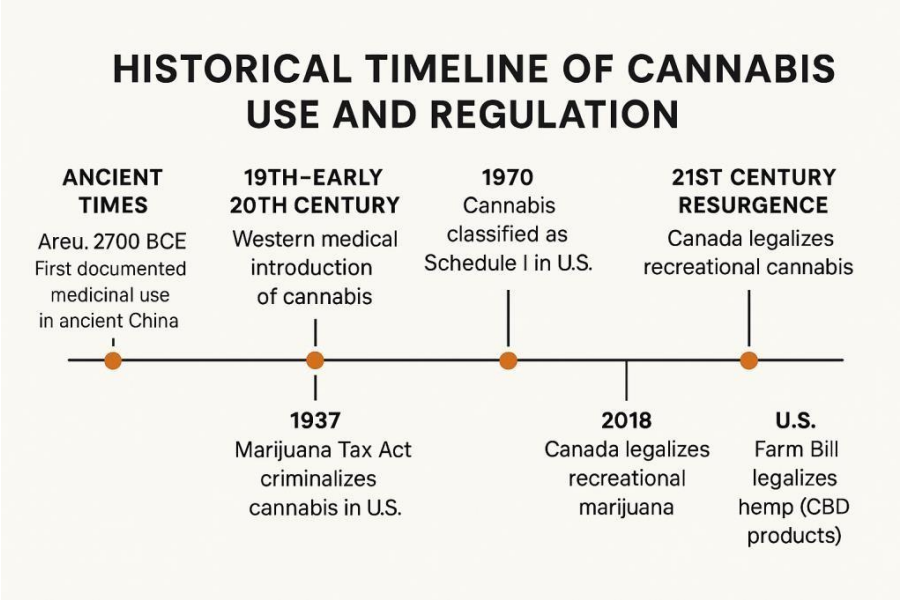



***Figure 2:*** *Historical Timeline of Cannabis Use and Regulation*

**Prohibition and Stigma**

The 20th century witnessed widespread prohibition driven largely by socio-political factors and classification as a narcotic [1, 4, 11, 12]. The US Schedule I classification imposed strict regulatory barriers, impeding clinical research despite patient demand [1, 8, 10]. This era fostered significant stigma, limiting cannabis research and use even as public acceptance sometimes preceded validation, as seen in Canada [4, 18, 28].

**Modern Resurgence**

Recent decades marked a resurgence driven by legislative reforms [e.g., US Farm Bill 2018 legalizing hemp-CBD [30]], shifting public attitudes, patient demand, market expansion [including OTC CBD [13]], and the opioid crisis [1, 6, 11, 13]. Legalization in places like Canada, Denmark, and Israel prompted new interest, particularly for cancer, MS, and neuropathic pain [4, 28]. The trend for research has now shifted towards specific conditions [2,4], cannabinoids [8, 13, 19-20], patient groups [11, 21, 30], specific delivery methods [14, 17], safety [10-12], and pharmacokinetics [15]. Despite of promising results from some studies [2, 6, 14], there is a need for better and more rigorous evidence [11] because of inconsistent results [3, 5, 18, 20].

**The Science of Cannabis in Pain Management**

***Cannabinoid Mechanisms***

The therapeutic rationale for cannabis in pain involves its interaction with the endocannabinoid system [ECS] [2, 3]. Key phytocannabinoids like THC act as partial agonists at CB1 [primarily CNS] and CB2 [primarily immune] receptors, influencing neurotransmission, inflammation, and pain perception [3, 10, 28]. CBD, conversely, is non-intoxicating and exhibits more complex pharmacology, acting as a negative allosteric modulator at CB1 receptors and interacting with various other targets [e.g., serotonin 5-HT1A, TRPV1, GABAA, PPARγ] [8, 10, 13]. CBD may also enhance endocannabinoid tone and potentially mitigate some of THC's adverse psychotropic effects [8, 13, 28, 29].

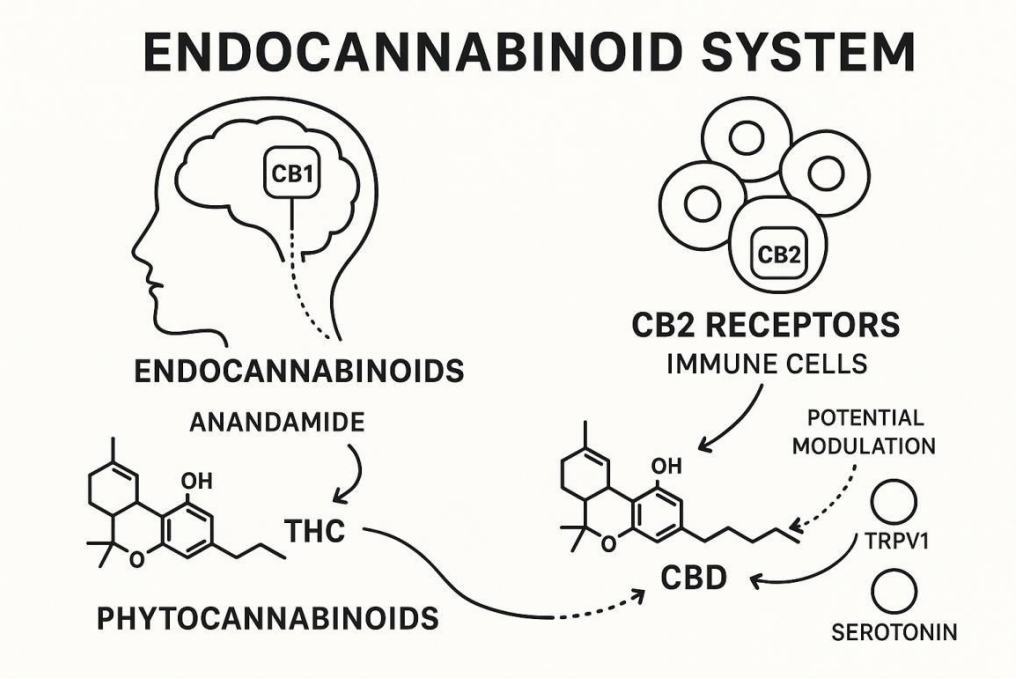



***Figure 3:*** *Simplified Endocannabinoid System [ECS] Diagram showing Receptors and Cannabinoid Interactions*

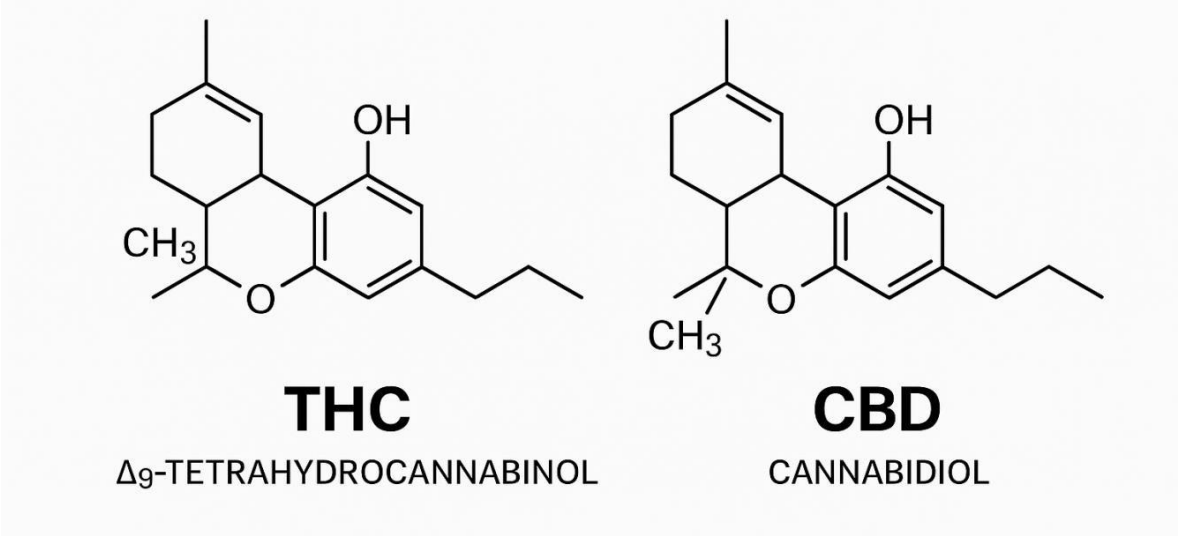



***Figure 4****: Chemical Structures of THC and CBD*

The interplay between THC, CBD, and potentially over 100 other phytocannabinoids and terpenes within the plant [the "entourage effect"] is hypothesized to contribute to the overall therapeutic profile, modulating nociceptive and inflammatory pathways in ways distinct from isolated compounds [2]. Formulations often leverage specific THC:CBD ratios [e.g., 1:1 in nabiximols, 1:6 in some studies] aiming to optimize this balance between efficacy and tolerability [22, 29].

### *Evidence of Efficacy*

Clinical evidence for the efficacy of cannabinoids in chronic pain remains inconsistent. Systematic reviews often report mixed findings; for example, Filippini et al. found only a small, statistically significant reduction in MS-related pain [MD -0.54 on a 0-10 scale], with low certainty evidence [22], while Solmi et al.'s umbrella review noted moderate pain reduction across RCTs but cautioned about psychological adverse events [11]. Specific formulations like nabiximols show some promise in cancer pain and opioid-refractory situations [4], though evidence in MS/SCI spasticity and pain remains modest [4, 28].Individual studies offer glimpses of potential benefit in certain populations. Mazza et al. documented significant improvements in pain and disability in fibromyalgia patients unresponsive to

conventional treatments [2]. Bassat et al. observed reduced pain severity and improved well-being in end-stage kidney disease patients, although the study lacked power for definitive efficacy conclusions [29]. Aviram et al.'s large cohort study reported a clinically modest [~20%] average pain reduction over 12 months [6], while Almog et al. found similar pain reduction and improved QoL in older adults using a controlled inhaler device [14].However, null or contradictory findings are prevalent. RCTs have failed to show significant benefit over placebo in peripheral neuropathic pain [3], HIV-associated neuropathic pain [using CBDV] [20], and for pain scores in sickle cell disease [though mood improved] [9]. Low-dose CBD [<300mg/day] appears to have weak analgesic evidence [13], and one experimental study even reported increased pain intensity ratings with CBD [19]. Furthermore, cannabinoids are generally not recommended for *acute* postoperative pain due to limited efficacy and potential risks identified in systematic reviews [23]. This discrepancy between some positive findings [often in observational or specific contexts] and negative RCT results underscores the current evidentiary conundrum.

**Table 1.** Summary of Efficacy Findings for Key Conditions

| Condition | Cannabinoid/ Formulation Tested | Key Efficacy Finding | Evidence Certainty/Study Type | Reference[s] |
|---|---|---|---|---|
| **Chronic Pain [General]** | Various Cannabinoids | Moderate pain reduction across RCTs [GRADE High]; Mild-to-moderate improvement [20% reduction] in cohort | Umbrella Review [11]; Cohort Study [6] | *6, 11* |
| **Fibromyalgia** | THC-dominant / Hybrid Cannabis | Significant reduction in pain/disability; >34% had ≥50% pain relief | Retrospective Case Series [2]; SR/MA [26] | *2, 26* |
| **Multiple Sclerosis [MS]** | Nabiximols [1:1 THC:CBD] / Various | Small pain reduction [MD -0.54], low certainty; Modest effects on pain/spasticity | Cochrane SR [22]; Review [28] | *22, 28* |

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|---|---|---|---|---|
| **Cancer Pain** | Nabiximols / Various | Potential benefit [e.g., 30% pain reduction], esp. opioid-refractory; Reduced opioid use | Review [4]; Cochrane Reg/SR Summary [7] | *4, 7* |
| **Peripheral Neuropathy** | Oral THC/CBD/Combo | No significant pain relief vs placebo | RCT [3] | *3* |
| **HIV-Neuropathy** | CBDV | No significant pain relief vs placebo | RCT [20] | *20* |
| **Rheumatoid Arthritis** | Cannabis-derived / Synthetic | Modest improvement in disease activity, minimal pain relief | Review/Summary [5] | *5* |
| **Sickle Cell Disease Pain** | Inhaled Cannabis | No significant reduction in pain scores; Improved mood interference | RCT [9] | *9* |
| **Osteoarthritis [Hand]** | Transdermal CBD | Feasibility demonstrated [Open-label] | Feasibility Trial [17] | *17* |
| **End-Stage Kidney Disease** | THC:CBD [1:6] Oral Extract | Reduced pain/symptom severity [VAS, BPI]; Improved sleep/well-being [Underpowered] | Feasibility RCT [29] | *29* |

| | | | | |
|---|---|---|---|---|
| **Acute Postoperative Pain** | Various Cannabinoids | No significant clinical benefit vs standard care; Potential increased pain/hypotension | SR/MA [23] | *23* |
| **Experimental Pain [Healthy]** | Oral CBD [Range of doses] | No consistent effect on pain threshold/tolerance; Increased pain intensity ratings | RCT [19] | *19* |

*SR: Systematic Review; MA: Meta-Analysis; RCT: Randomized Controlled Trial; MD: Mean Difference; VAS: Visual Analog Scale; BPI: Brief Pain Inventory.*

### *Limitations of Evidence*

The interpretation of efficacy data is significantly hampered by pervasive methodological limitations across the literature. A frequent issue is the lack of large, well-powered, long-term RCTs; many existing trials have small sample sizes [e.g., n=15 [29]], short durations [often <16 weeks [22]], high dropout rates, or lack appropriate active comparators [11, 9, 22, 28, 29]. The absence of standardized cannabis formulations and dosing regimens represents a fundamental challenge, leading to substantial heterogeneity in interventions [THC/CBD content, ratios, delivery methods] that complicates cross-study comparisons and meta-analyses [11, 9, 22]. Methodological quality varies, with GRADE assessments often rating evidence certainty as low or very low due to high risks of bias [e.g., inadequate blinding, selective outcome reporting] and unexplained inconsistency in results [22, 24]. The lack of long-term follow-up data limits understanding of sustained efficacy and chronic risks [29]. Publication bias and incomplete reporting within studies [e.g., regarding concomitant medications or prior cannabis use] may further skew the available evidence [24]. Finally, reliance on patient-reported outcomes in open-label or retrospective studies introduces potential observer-expectancy bias [2, 22]. These limitations collectively weaken the foundation for definitive clinical recommendations.

### Clinical Benefits: A Viable Option

Cannabis-based therapies garner attention for potential benefits in chronic pain, particularly regarding analgesia, opioid reduction, and patient satisfaction, though applicability remains debated.

### *Pain Relief*

Evidence suggests cannabis can provide modest pain relief in specific chronic conditions, though not universally. Studies report statistically significant, albeit often small, reductions in neuropathic pain associated with MS [22, 25] and notable improvements in fibromyalgia pain and disability, particularly in treatment-refractory patients [2, 26]. Potential benefits in cancer-related pain are also suggested [4, 16]. Cohort studies show average pain intensity reductions around 20% over 12 months [6] or ~2 points on a 10-point scale [14], suggesting modest but potentially meaningful effects for some individuals. Specific formulations like nabiximols [4, 22] or moderate-dose CBD [300-400mg/day] [13] show some effect in certain contexts. However, this contrasts sharply with high-quality trials showing lack of benefit in peripheral neuropathy [3], HIV-neuropathy [20], or rheumatoid arthritis [5], highlighting the condition-specific and often limited nature of the analgesic effect.

### *Opioid Sparing*

Reducing reliance on opioid medications is a frequently cited potential benefit, particularly relevant amidst the opioid crisis. Several observational studies and reviews report associations between medical cannabis initiation and subsequent decreases in opioid consumption or complete cessation [4, 6, 18, 28]. Clinically significant reductions in MEDD [e.g., 42% reduction in Aviram et al. [6]] or high rates of opioid discontinuation/reduction [e.g., ~40% in Almog et al. [14]] have been observed in some cohorts. Observational data from fibromyalgia patients [2] and case reports in osteoarthritis or post-surgical pain [3, 27] further support this potential. This opioid-sparing effect is clinically significant given the risks associated with long-term opioid therapy [6, 18]. However, the effect is not guaranteed, as some studies found no significant change in opioid use [9], and importantly, adding cannabinoids like THC to opioids does not necessarily enhance analgesia and may increase adverse events [18].

### *Patient Perspectives*

Patient-reported outcomes and perspectives often paint a more positive picture than objective efficacy data suggest. High patient interest exists, driven partly by dissatisfaction with conventional treatments and concerns about opioid safety, particularly among older adults [11, 30]. Surveys and qualitative data indicate that many patients report improvements in overall quality of life [28, 14], a greater sense of control over their pain [13], and high satisfaction with cannabis therapy [14]. Some patients prefer cannabis due to a perceived better side-effect profile compared to conventional medications [12]. Beyond direct pain relief, improvements in common comorbid symptoms like sleep disturbances, appetite, anxiety, and general well-being are frequently reported [2, 29], contributing to positive patient experiences. Preferences for specific formulations [e.g., oils over decoctions] based on taste or convenience also emerge [2].

### *Case Studies and Specific Applications*

Real-world applications and specific use cases are illustrated through various study designs. Retrospective case series provide insights into effectiveness in conditions like fibromyalgia [2, 29]. Cohort studies track outcomes in broader chronic pain groups [6] and specific populations like the elderly [14]. RCTs rigorously evaluate specific interventions, such as inhaled cannabis for sickle cell disease [9], oral capsules for neuropathy [3], selective-dose inhalers for controlled delivery [14], or isolated cannabinoids like CBDV for HIV-pain [20]. Feasibility studies explore novel delivery methods like transdermal CBD for osteoarthritis [17]. Ongoing research is planned via protocols targeting adolescent migraine [21] or fracture healing [19]. Case reports offer snapshots of success in challenging situations like refractory post-surgical pain [27] or managing symptoms in hemodialysis patients [3]. These diverse examples underscore the wide range of conditions and contexts where cannabis is being actively investigated, although robust evidence supporting routine use in many of these areas is still lacking.

### Clinical Challenges: A Conundrum?

Despite potential benefits, significant clinical challenges hinder the widespread, evidence-based application of medical cannabis, contributing to the clinical conundrum.

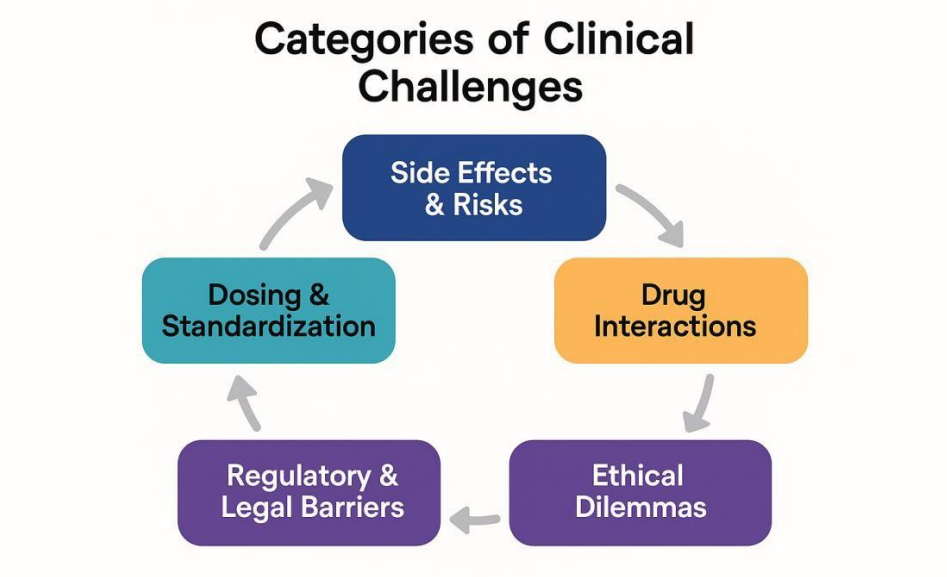

***Figure 5:*** *Clinical Challenges Categories*

***Side Effects and Risks***

Adverse effects [AEs] are frequently reported and represent a primary clinical challenge, although they are often mild to moderate and may diminish with tolerance or dose adjustment [10, 29]. Common AEs include dizziness, somnolence/sedation, fatigue, dry mouth, and nausea [2, 10, 11, 12, 29]. Cognitive effects, such as mental "clouding," impaired memory, and reduced attention, are also prevalent and raise concerns about functional capacity and safety, particularly regarding driving or operating machinery [10, 12, 32]. Psychiatric effects, including confusion [reported in up to 37% of fibromyalgia patients in one study [2]], restlessness, anxiety, and, more rarely, hallucinations [especially linked to accidental overdose [29]], are significant risks requiring careful screening and monitoring [2, 10, 11, 22, 29]. Although CBD is often perceived as having a better safety profile than THC [2], dose-dependent mood alterations and abuse liability concerns have been noted even with CBD in experimental settings [19]. Cardiovascular effects like hypotension [particularly noted postoperatively [23]] or tachycardia require caution, especially in patients with pre-existing conditions like ESKD [29]. The potential for long-term risks, such as sustained cognitive decline or dependency, remains debated and requires further study [10, 11]. Concerns about potential hepatotoxicity have also been raised, particularly with illicit or unmonitored use [29]. The overall AE profile necessitates individualized risk assessment, slow titration, ongoing monitoring, and clear patient education [10, 12, 29].

***Table 2.*** *Summary of Common Adverse Events Reported*

| Adverse Event Category | Specific Examples Reported | Notes on Frequency/Severity | Reference[s] |
|---|---|---|---|
| **Neurological/CNS** | Dizziness, Somnolence/ Sedation, Fatigue, Cognitive Impairment ["Clouding", Memory Issues], Headache | Common, Often Mild-Moderate, May resolve with dose adjustment/tolerance | *2, 10, 11, 12, 22, 29, 32* |
| **Psychiatric /Psychological** | Confusion, Restlessness, Anxiety, Mood Alterations, Euphoria, Hallucinations [rare, esp. overdose] | Increased risk vs placebo [Low-certainty evidence]; Confusion up to 37% [FMS study] | *2, 10, 11, 19, 22, 29* |
| **Gastrointestinal** | Nausea, Vomiting, Dry Mouth | Common | *2, 10, 12, 29* |
| **Cardiovascular** | Hypotension, Tachycardia | Possible, esp. post-op or with overdose; Caution in specific populations [e.g., HD] | *23, 29* |

| | | | |
|---|---|---|---|
| **Abuse Liability/Dependency** | Potential for dependency/ abuse noted | Concern raised, esp. long-term use; CBD lower potential than THC | *10, 11, 19, 27* |
| **Other** | Impaired Alertness/Reaction Time [Workplace Safety Concern], Falls [esp. elderly], Potential Liver Enzyme Impact | Concerns raised in reviews/specific studies | *10, 12, 29* |

***CNS:*** *Central Nervous System; FMS: Fibromyalgia Syndrome; HD: Hemodialysis. Note: Frequency/severity notes are based on qualitative descriptions in the source texts; quantitative data is often limited or inconsistent across studies*.

### *Dosing and Standardization*

The profound lack of standardization in both cannabis products and clinical dosing protocols represents a fundamental obstacle to evidence-based practice [3, 6, 11, 13]. Products vary immensely in cannabinoid content [THC, CBD, minor cannabinoids], ratios, terpene profiles, and formulations [e.g., flower, oil, edibles, sprays, topicals], making it difficult to ensure consistent effects or compare study results [5, 6]. Effective doses reported in studies span a vast range [e.g., MC flower 200-400mg/day [2]; CBD from <100mg to >1000mg/day [13, 30]], with little consensus on optimal targets for specific conditions. Furthermore, the burgeoning OTC CBD market often lacks regulatory oversight, leading to inaccurate labeling and products with dosages potentially below therapeutic thresholds [13, 30]. Clinical practice typically defaults to individualized titration ["start low, go slow"], adjusting dose based on patient response and tolerability [15, 26, 29], often using imprecise methods like counting drops or sprays [2, 21, 29]. While novel delivery systems like selective-dose inhalers aim to improve precision [14], establishing standardized, validated dosing regimens remains a critical unmet need [5, 6].

### *Drug Interactions*

The potential for pharmacokinetic and pharmacodynamic drug interactions is a significant clinical concern, yet robust clinical data remain limited. Cannabinoids, particularly CBD, are known to interact with the cytochrome P450 enzyme system, potentially altering the metabolism and plasma concentrations of various concurrently administered drugs, including common medications like anticoagulants [e.g., warfarin], anticonvulsants, and antidepressants [10, 13, 30]. Additive sedative effects are possible when cannabis is combined with other CNS depressants like benzodiazepines or alcohol [14]. Co-administration with opioids requires particular caution; while opioid-sparing effects are sought, direct combination may increase adverse events without improving analgesia [18]. Current clinical studies often mitigate this risk by excluding patients on potentially interacting medications or implementing careful monitoring protocols [29]. However, the lack of comprehensive clinical interaction data necessitates a cautious approach, involving thorough medication review and close patient monitoring when initiating cannabis therapy [10, 29].

### *Regulatory and Legal Barriers*

The complex and inconsistent legal status of cannabis globally creates substantial regulatory hurdles for research and clinical practice [1, 8, 10, 11]. In many regions, cannabis remains a controlled substance, hindering large-scale, multi-site clinical research [especially international trials] and complicating the development and implementation of standardized clinical guidelines [10, 11, 27]. Even where medical use is legal [e.g., Canada, parts of US, Italy, Israel [2, 4, 29, 30]], navigating specific licensing requirements [e.g., Ministry of Health approvals [29]], stringent ethics protocols, potential supply interruptions [2], and administrative burdens present practical challenges for researchers and clinicians [2, 27, 29]. Furthermore, the

lack of robust federal regulation and quality control standards for many products, particularly OTC CBD, leads to inconsistencies and potential safety concerns [30]. Addressing issues related to workplace safety, defining impairment, and establishing clear return-to-work protocols for medical cannabis users also remains an unresolved regulatory challenge [12].

### *Ethical Dilemmas*

The use of medical cannabis is embedded in several ethical considerations. Prescribing a treatment with an inconsistent evidence base, particularly regarding long-term safety and efficacy, poses dilemmas for clinicians balancing potential benefits against known and unknown risks [10, 11, 19]. Obtaining truly informed consent is complex when evidence is conflicting and public perception varies widely. Particular ethical scrutiny is needed when considering use in vulnerable populations, such as adolescents [where research protocols require careful oversight [21]], the elderly [potential for falls, cognitive effects, polypharmacy [14]], or individuals with psychiatric conditions or substance use histories [10, 27]. The potential for abuse or diversion remains a concern [11]. Furthermore, reliance on subjective patient-reported outcomes, especially in open-label settings susceptible to expectancy bias, raises ethical questions about treatment validation and continuation [2]. Balancing patient autonomy and demand with professional responsibility and the principle of non-maleficence is central to the ethical use of medical cannabis.

## Comparative Analysis: Cannabis vs. Conventional Treatments

The therapeutic landscape for pain management has evolved significantly, with conventional options like opioids, NSAIDs, and adjuvants forming the foundation. Increasing interest in medical cannabis prompts comparative investigations into its role alongside or in place of traditional therapies.

### *Opioids*

Opioids are potent analgesics commonly prescribed for moderate to severe pain but are associated with substantial risks, including tolerance, dependence, and respiratory depression [18]. Although effective, long-term opioid use [prescribed to as many as 50% of patients receiving hemodialysis [HD]] can lead to negative effects like nausea, constipation, and excessive somnolence [29]. Opioids are also associated with higher risks of falls, fractures, morbidity, and mortality, particularly in HD patients where altered pharmacokinetics [decreased renal clearance causing accumulation, increased clearance during dialysis causing withdrawal] heighten risks [29]. For conditions like neuropathic pain or fibromyalgia, opioids are often reserved for severe, intractable cases after initial therapies [e.g., gabapentinoids, antidepressants] prove inadequate or cause intolerable side effects [2, 6, 29]. While historically first-choice for cancer pain due to effectiveness in nociceptive pain [4], increasing evidence, albeit low certainty, suggests medical cannabis might have fewer serious long-term adverse effects [e.g., cognitive impairment, dependence] compared to opioids, though head-to-head comparisons are needed [27]. Furthermore, co-administration of THC with hydromorphone suggested a potential therapeutic advantage for multimodal approaches in chronic pain [18].

### *NSAIDs and Adjuvants*

There is a significant clinical need for safer pain relief alternatives, especially for patients with contraindications to NSAIDs, such as those with end-stage kidney disease [ESKD] where NSAIDs are generally avoided due to nephrotoxicity [5, 11, 29]. Acetaminophen is typically used for mild pain in this population [29]. Other conditions like multiple sclerosis [MS] often involve adjuvants like baclofen, tizanidine, anticonvulsants, or antidepressants to manage symptoms like spasticity and neuropathic pain, but efficacy may be limited and side effects poorly tolerated [4, 22]. Cannabis, particularly CBD with its demonstrated anti-inflammatory activity in preclinical arthritis models [17, 25], represents a potential alternative, although direct clinical comparisons with NSAIDs or standard adjuvants are lacking. The endocannabinoid system is a promising therapeutic target for pain and related symptoms like nausea and anorexia [29]. Interestingly, CBD may enhance THC's analgesia while mitigating psychotropic effects [9]. However, evidence for CBD analgesia is inconsistent, with some studies showing dose-dependent effects while others find no benefit or even increased pain responses [19]; chronic use may be more beneficial than acute use [19]. Sex differences in response to cannabinoid analgesia may also exist [16]. Furthermore, conventional analgesics like NSAIDs and opioids have potential negative impacts on bone healing [31], an area where cannabis effects are less studied.

### *Multimodal Therapy*

Cannabis is often positioned or studied within a multimodal therapy framework, frequently used as an add-on to existing stable analgesic regimens rather than as monotherapy [9, 28]. Its potential for synergistic

effects with opioids, while largely anecdotal [4], remains an area of interest, though clinical trials highlight complexities [18]. The ability of cannabis to address common comorbid symptoms in chronic pain patients—such as nausea, poor appetite, sleep disturbances, or anxiety [2, 29, 31]—may enhance overall treatment outcomes when combined with conventional analgesics targeting nociception or specific pain pathways. The development of delivery systems allowing for controlled, customizable dosing, like metered-dose inhalers [14], supports its potential integration into personalized multimodal plans. Cannabis is also being explored for pediatric chronic pain conditions like headache [21] and is used alongside other therapies for symptoms like spasticity in MS [22] or refractory symptoms in dialysis patients [29]. Its established efficacy in reducing seizures in certain epilepsy syndromes further illustrates its role alongside other treatments [11].

## Future Directions & Conclusion

Significant research gaps persist despite growing patient interest and preliminary evidence regarding medical cannabis for chronic pain [6, 11]. While preclinical studies consistently demonstrate antinociceptive and anti-inflammatory activity of cannabinoids in animal models [16, 25], translating these findings to human clinical efficacy remains challenging, yielding mixed results. For instance, studies investigating specific cannabinoids like CBDV for HIV-neuropathic pain [20] or various CBD doses for experimental pain [19] found them safe but largely ineffective, sometimes even increasing pain scores, highlighting a translational gap.Consequently, there is an urgent need for more rigorous, large-scale, long-term randomized clinical trials [RCTs] [11, 28]. These trials must evaluate specific cannabinoids [THC, CBD, minor cannabinoids], well-defined formulations, dosages, and delivery mechanisms across diverse chronic pain conditions. Prioritizing patient-centered outcomes beyond simple pain scores is crucial. Investigating novel delivery systems, such as metered-dose inhalers [e.g., Syqe [14]], which may offer controlled analgesia with minimal cognitive impairment [19, 14], requires further pharmacokinetic and clinical assessment [15]. Additionally, research must better explore differential responses based on patient characteristics like sex [16], age, genetic factors, and comorbidities [6]. Head-to-head comparisons with standard-of-care analgesics are also essential.

### *Personalized Medicine: Tailoring Cannabinoid Therapy*

The marked interindividual variability in response to medical cannabis underscores the need for personalized approaches [6, 15, 29]. Advances in pharmacogenomics, although not extensively detailed in the core reviewed literature here, are beginning to explore genetic polymorphisms [e.g., in CYP enzymes like CYP2C9 and CYP3A4, or cannabinoid receptors like CNR1 [34]] that may influence THC/CBD metabolism, endocannabinoid signaling, and ultimately, therapeutic outcomes and adverse event profiles. The aim is to eventually leverage such knowledge, alongside detailed clinical phenotyping, to tailor cannabinoid profiles [THC:CBD ratios, terpene content], dosage forms, and administration routes to individual patient needs, thereby optimizing efficacy while minimizing risks [6, 15, 29]. Current practice already relies heavily on individualized titration [29], but a more scientifically guided personalization is a key future direction.

### *Role of Artificial Intelligence*

Artificial Intelligence [AI] and machine learning [ML] are emerging as powerful tools to navigate the complexities of medical cannabis therapy for chronic pain [34]. Recent research, such as the work by Visibelli et al. [34], demonstrates the potential of ML models [e.g., Random Forest classifiers] to predict patient-specific outcomes like therapy dropout by integrating comprehensive datasets encompassing genetic, clinical, and pharmacological information. Such models have achieved robust performance [e.g., mean accuracy of 80%, AUC of 0.86] in identifying key predictors of treatment adherence or discontinuation [34]. For instance, high final pain scores [VAS] and elevated THC dosages were identified as significant predictors of dropout, whereas baseline therapeutic benefits and specific genetic markers [e.g., rs1049353 polymorphism in CNR1] were associated with improved adherence [34]. Techniques like SHapley Additive exPlanations [SHAP] analysis are being used to pinpoint the most influential factors driving these predictions [34]. Other applications include leveraging patient-reported outcomes from apps [e.g., Strainprint, as explored by a study not included in the primary reference list but indicative of the trend] to recommend specific strains or formulations. AI-driven pharmacovigilance tools also hold promise for early detection of unusual side effect patterns or potential misuse.

### *Policy Recommendations*

Regulatory and policy frameworks need refinement to address the complexities of medical cannabis. A nuanced approach distinguishing between cannabinoids like THC and CBD based on psychoactivity and abuse potential [CBD generally having lower potential [19]] could inform scheduling and accessibility policies [31]. Development

of robust pharmacovigilance systems, potentially utilizing electronic health platforms, is critical for systematically documenting long-term outcomes and adverse effects, thereby enhancing patient safety and informing regulatory decisions [27]. Public and healthcare professional education campaigns are needed to disseminate accurate, evidence-based information, counteracting misinformation [11, 13]. As suggested by Campbell et al. [18], clearer communication strategies and enhanced clinical training are vital for the responsible integration of cannabinoids into pain management. Furthermore, establishing clear regulations for quality control, standardized testing, and transparent labeling, especially for the largely unregulated OTC CBD market, is imperative for consumer protection [13, 30]. Addressing workplace safety concerns through defined impairment guidelines is also necessary [12].

### *Clinical Guidelines*

Current clinical practice guidelines for medical cannabis in chronic pain are often underdeveloped, inconsistent, or non-existent, lagging behind patient use and legislative changes [5, 11]. Future guidelines must be dynamic, adapting cautiously as higher-quality evidence emerges. Based on current limited evidence, cannabis-based therapies might be considered for chronic pain refractory to conventional treatments, often favoring balanced THC:CBD or CBD-dominant formulations initially to mitigate psychoactive effects, especially in naive users or those with psychiatric risks [2, 4, 11, 29]. Route of administration significantly impacts pharmacokinetics; inhaled forms offer rapid onset but may pose respiratory risks, while oral routes have slower onset and greater variability [14, 15]. Regardless of the approach, ongoing monitoring for adverse events [including cognitive and psychiatric effects [10]], functional improvement, and potential drug interactions [18] is crucial. While some cognitive tolerance may develop [32], initial vigilance is key. Therapy must be highly individualized, considering patient-specific factors [age, sex, comorbidities, metabolism] and treatment goals [6, 16].

### *Summary*

Medical cannabis demonstrates moderate, albeit inconsistent, potential in the complex landscape of chronic pain management. Evidence suggests possible benefits, particularly for neuropathic pain, fibromyalgia, and potentially as part of opioid-sparing strategies [6, 2, 22]. Modest reductions in pain intensity and improvements in secondary outcomes like sleep and mood are reported in several studies [6, 8, 29]. However, the field is hampered by significant heterogeneity in products, dosing, and study quality, making definitive conclusions difficult [11, 22]. CBD generally appears safer but has inconsistent analgesic efficacy [13, 19], while THC may offer more potent analgesia but carries a greater risk of impairing side effects [10, 18]. The overall picture remains one of cautious optimism constrained by significant evidentiary gaps and clinical challenges.

### *Final Reflection*

Despite its widespread use and growing acceptance, medical cannabis remains at a crossroads regarding scientific validation and clinical integration [11]. The contrast between clinical hesitancy [driven by inconsistent evidence and safety concerns] and policy enthusiasm or patient demand highlights a significant gap [4, 11]. Chronic pain patients urgently need safe and effective therapeutic options. Resolving the "conundrum" of medical cannabis requires bridging this gap between anecdotal reports or preliminary findings and robust scientific validation. This necessitates a concerted, transparent, and collaborative effort involving researchers committed to rigorous study designs, policymakers developing informed regulations, healthcare professionals equipped with evidence-based knowledge, and patients engaged in shared decision-making [5, 11, 12].

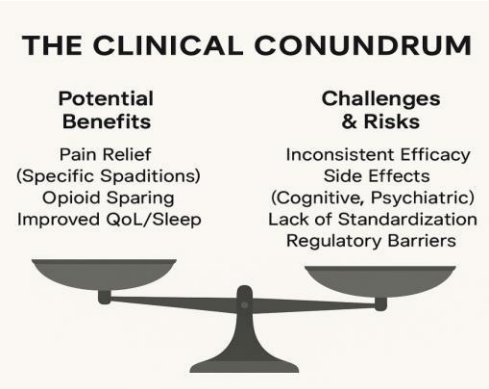

***Figure 6:*** *Conceptual Diagram - The Clinical Conundrum Balance Scale*

***Call to Action***

Moving forward requires focused action from multiple stakeholders. Researchers must prioritize well-designed RCTs evaluating specific cannabinoids, formulations, and delivery routes for defined pain conditions, including long-term follow-up and active comparators [11, 13, 28]. Clinicians should approach cannabinoid therapy cautiously, integrating it into personalized, multimodal treatment plans guided by the best available evidence, careful patient selection, and ongoing monitoring [6, 11]. Regulators need to differentiate between cannabinoids where appropriate, enforce stringent quality control and standardization for all medical products, and ensure transparent labeling [13, 30]. Educators have a vital role in incorporating objective, evidence-based medical cannabis training into healthcare curricula to equip providers to critically appraise research and counsel patients effectively [18]. Only through such coordinated efforts can the true potential and limitations of medical cannabis for chronic pain be fully elucidated.

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