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ADVANCES IN CANNABINOID-BASED PAIN MANAGEMENT: EFFICACY AND EVIDENCE

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ABSTRACT

Introduction and Purpose: Chronic pain is a significant global health challenge, and its management is complicated by the substantial risks associated with conventional therapies such as opioids. Cannabinoids, targeting the endocannabinoid system, have been developed as effective therapeutic options. This systematic review assesses current research evidence about cannabinoid safety and effectiveness for managing various chronic pain conditions to establish their worth in modern pain management.

Main Findings: The evidence for cannabinoid efficacy is highly condition-specific. Moderate-quality evidence supports cannabinoid-based medicines for chronic neuropathic pain, demonstrating reduced pain intensity and improved sleep. The strongest evidence exists for spasticity-related pain in multiple sclerosis, for which nabiximols is an approved treatment. Key guidelines recommend that cannabinoids have no efficacy for cancer pain. There is currently no clinical evidence for providing relief of inflammatory pain, such as fibromyalgia. Evidence also supports an adjuvant role via a potential "opioid-sparing" effect. The safety profile includes moderate side effects, which include dizziness and somnolence, and does not carry the lethal respiratory depression risk associated with opioids.

Conclusion: Cannabinoids provide a new pharmacological approach, but they do not work as a universal analgesic. The existing evidence supports their utility as adjunctive therapy for certain, refractory conditions — especially neuropathic pain and MS-related spasticity. Compared to opioids, their favorable safety profile would indicate they could represent an important adjunct for multimodal pain management. More large-scale trials using standardized formulations are required to specify their exact place they hold in evidence-based care.

KEYWORDS

Cannabinoids, Chronic Pain, Pain Management, Cannabis, THC, CBD

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1. Introduction and purpose

Chronic pain is one of the most significant challenges of modern medicine. The medical community acknowledges this condition as both a painful symptom and an independent disease entity. The condition results in major life quality deterioration and complete disability while creating substantial financial expenses for society. The worldwide prevalence of chronic pain affects 31% of the adult population according to a recent extensive systematic review and meta-analysis, which confirms its position as a leading cause of disability [1]. The European population shows similar rates of chronic pain, which makes it a leading cause of doctor visits and work absences [2]. Chronic pain syndromes, such as neuropathic pain, osteoarthritis, or fibromyalgia, are characterized by a complex pathophysiology that significantly complicates effective and safe treatment.

The condition known as "high-impact chronic pain" creates major limitations for patients who need to perform social activities and work and maintain self-care responsibilities. It leads to higher rates of severe depression and anxiety disorders, which make disability worse for patients [3].

The World Health Organization (WHO) developed the analgesic ladder for cancer pain treatment, which serves as the basis for standard pharmacological chronic pain management. The first line of treatment for chronic pain management includes non-opioid medications, which include NSAIDs and paracetamol (acetaminophen). The addition of weak opioids such as tramadol or codeine becomes necessary when pain symptoms worsen or fail to respond to initial treatment. The third-line treatment for severe unmanageable pain includes strong opioids, such as fentanyl and oxycodone [4].

The established treatment approach for chronic pain management contains multiple negative aspects. The extended use of NSAIDs leads to major side effects, which damage the gastrointestinal system and kidneys and increase the risk of cardiovascular diseases [5]. Opioid treatment for non-cancer pain has led the

pharmaceutical industry to generate a worldwide opioid epidemic, which has now reached the level of addiction and fatal overdose situations [6]. The existing risks demand immediate development of new therapeutic methods that can replace or enhance current pain management treatments.

Cannabinoids have emerged as a promising area of research in response to these therapeutic challenges. These compounds have been used for medical purposes throughout history, while scientists today conduct thorough studies to determine their effectiveness in treating different types of chronic pain.

The therapeutic potential of exogenous cannabinoids is predicated on their interaction with the endocannabinoid system (ECS), a neuromodulatory system integral to physiological homeostasis. The ECS contains two main G-protein coupled cannabinoid receptors, which are CB1 receptors found in central areas and CB2 receptors located in peripheral regions, and two main endogenous lipid-based compounds anandamide and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for their production and degradation [7]. The ECS functions as a critical homeostatic regulator in the context of nociception. The synthesis of endocannabinoids occurs in postsynaptic neurons through demand-based processes, which then travel to presynaptic CB1 receptors to block nociceptive neurotransmitter release and reduce pain transmission [8].

The two main phytocannabinoids from Cannabis sativa plants known as THC and CBD operate in separate ways to affect the endocannabinoid system. The analgesic and psychoactive properties of THC emerge from its ability to activate CB1 and CB2 receptors as a partial agonist, which mimics the action of natural endocannabinoids. CBD shows a wide range of therapeutic actions through its weak binding to cannabinoid receptors, but it does not occupy their traditional binding sites. The therapeutic benefits of CBD stem from its ability to boost endocannabinoid signalling through its inhibition of fatty acid amide hydrolase, which increases anandamide levels in the synapses [9]. The different ways THC and CBD interact with the body create a solid scientific basis for creating new pain management medications [10].

This review critically examines the current evidence on the use of cannabinoids in treating chronic pain in response to these therapeutic challenges. It specifically evaluates their efficacy in conditions such as neuropathic pain, fibromyalgia, and cancer-related pain, while also assessing their safety profile and potential role as an alternative or adjuvant therapy.

2. Methodology

The search was performed using PubMed between August and October 2025 and was restricted to articles published between 2005 and 2025. The search strategy employed a combination of Medical Subject Headings (MeSH). The primary search terms included "Cannabinoids"[MeSH] OR "Cannabis"[MeSH] OR CBD OR THC OR Nabiximols OR Sativex) AND ("Pain"[MeSH] OR "Chronic Pain"[MeSH] OR "Cancer Pain")).

3. Results

3.1 Neuropathic Pain

A moderate body of evidence supports the use of certain cannabinoids for chronic neuropathic pain. A prominent meta-analysis found that both nabiximols (THC: CBD oromucosal spray) and inhaled cannabis significantly reduced pain intensity compared to placebo [11]. Synthetic cannabinoids, such as nabilone, have also shown some efficacy, but the evidence for their use in neuropathic pain is less consistent than that for nabiximols [8]. Beyond direct analgesia, studies consistently reported secondary benefits, including significant improvements in sleep quality [11, 12].

Although effective for a subset of patients, the clinical benefit must be weighed against a higher incidence of adverse events, most commonly dizziness, dry mouth, and somnolence [8]. Those side effects were generally rated as well tolerated, transient, and of mild-moderate magnitude and did not usually lead to withdrawal from the study. This is in marked contrast to withdrawal rates observed among other analgesics, including opioids, where withdrawal rates from treatment are around 33% [13].

The 2024 clinical practice guidelines issued a strong recommendation for the use of cannabinoid-based medicines (CBMs) for the management of neuropathic pain, supported by moderate-quality evidence. These guidelines recommend CBMs for managing central and peripheral neuropathic pain, as viewed through the broader lens of chronic pain management. Furthermore, the guidelines make a separate strong recommendation, also based on moderate-quality evidence, for using CBMs to manage neuropathic pain in people living with HIV who do not achieve an adequate response to other therapies [14].

3.2 Cancer-Related Pain

Key clinical practice guidelines like those from the National Comprehensive Cancer Network (NCCN) strictly set cannabinoids as an adjunct, not a baseline, therapy. According to NCCN guidelines, cannabinoids can be indicated as an adjunctive agent for patients with chronic or neuropathic pain poorly controlled by standard analgesics, or chemotherapy–induced nausea and vomiting (CINV) resistant to standard antiemetic agents [15].

This stance is reinforced and further specified by the 2024 American Society of Clinical Oncology (ASCO) guideline, which outlines a minimal therapeutic application. This guidance explicitly advises against using them for cancer-related pain but does call for their added use as a supplementary treatment in cases of adult CINV resistant to the standard antiemetic treatment. The guideline further recommends that synthetic cannabinoids such as dronabinol and nabilone—or a quality-controlled oral 1:1 THC:CBD extract—might be supplemented during this period [16].

This recommendation against the use of cannabinoids for pain is strongly supported by the 2023 Cochrane systematic review, which concludes with moderate confidence that both nabiximols and dronabinol are ineffective for moderate-to-severe cancer pain that does not respond to opioids. Additionally, CBD oil provides no additional pain control in advanced cancer when combined with specialized palliative care. These results highlight the absence of analgesic evidence and reinforce the overall advice against the use of cannabinoids for cancer pain [17].

Beyond the lack of efficacy, a significant clinical concern is the potential for drug-drug interactions. Cannabinoids, including CBD, can inhibit cytochrome P450 enzymes involved in the metabolism of a significant number of chemotherapeutic and immunotherapeutic agents [18]. This interaction carries the risk of altering drug concentrations, potentially increasing toxicity or reducing therapeutic efficacy, a key factor underpinning the cautious recommendations from oncology bodies.

Contextualizing these clinical findings in the context of the patients' experiences is crucial. While strong findings establishing no evidence of analgesic action are available, cannabinoids are still a frequently sought-after medication. A survey at a major US cancer centre reported that nearly a quarter of those surveyed were currently using cannabis mainly as a treatment for symptoms, but most did not report it to their oncologist [19]. This suggests an alarming disconnect between what is documented and the evidence-based clinical guidance.

3.3 Spasticity-Related Pain

The use of cannabinoids for managing spasticity is most robustly established in the context of multiple sclerosis (MS), particularly as conventional treatments often fall short. First-line options, including baclofen and benzodiazepines, often do not have a satisfactory effect, while other alternatives, like botulinum toxin type A, are only partially therapeutic [20]. Tetrahydrocannabinol (THC), a psychoactive phytocannabinoid with a potent CB1 receptor agonist that exerts the main therapeutic effect of cannabinoids [21]. Clinical evidence indicates that the mechanism involves modulation of cortical excitability, which leads to enhanced inhibitory control mechanisms in the spinal interneurons involved in the pathophysiology of spasticity [22]. In contrast, the presence of non-psychotropic cannabidiol (CBD) and CB2 receptor does not seem to matter as much in this condition, with solid evidence for its anti-inflammatory or neuroprotective effects in humans remains rare [23-25]. This clinical usage is well-described in evidence based on RCTs and systematic reviews [26-28]. Although the important meta-analysis demonstrated a large and significant benefit on the physician-rated Ashworth measure of clinical outcome, SMD (−1.78) [29], the evidence is arguably stronger on patient-reported consequences, and patients experience a remarkable quality of life difference and subjective symptom relief as a result of treatment [29]. Consequently, nabiximols is an approved treatment for moderate to severe MS-related spasticity in many countries [26, 29]. It is crucial to note that this strong evidence base is highly specific to MS. While a theoretical rationale exists for using cannabinoids in other neurological disorders like cerebral palsy, extensive research has not substantiated their clinical effectiveness in these conditions [30].

The evidence for the analgesic role of cannabinoids in spinal cord injury (SCI) is primarily driven by observational studies, which indicate significant subjective benefits despite being conducted on limited patient populations. For example, one trial found that 59% of individuals using cannabinoids for pain reported 'good' or 'very good' efficacy [31], while another study noted a self-reported mean pain relief of 6.62 out of 10 [32].

The apparent clinical importance may seem quite high for patients. Among over 25 pain treatment options, cannabinoids were rated the most effective analgesic; they offered substantially more relief than the usual agents, including NSAIDs, baclofen, and tricyclic antidepressants in a landmark study by participants [32]. This finding is reinforced by another study where 59% of users reported at least a 'good' effect on pain, further highlighting the strong patient preference for cannabinoids over other available treatments [31].

3.4 Inflammatory Pain (e.g., Rheumatic Diseases)

The evidence for cannabinoids in managing inflammatory and central chronic pain conditions remains largely inconclusive and insufficient for clinical recommendations. There is a notable gap between preclinical data and clinical outcomes for rheumatologic diseases such as rheumatoid arthritis. High-quality clinical evidence is scarce despite strong preclinical studies highlighting the anti-inflammatory properties of cannabinoids, particularly CBD. A systematic review of randomized controlled trials (RCTs) found inconsistent results for pain, joint swelling, or morning stiffness, concluding that current evidence does not support the recommendation of cannabinoids for these conditions [33, 34].

This formal conclusion that results from RCTs, however, is in stark contrast to what patients do. Cannabis use is common across this population, with nearly one in five patients claiming to use cannabis to control pain. This patient-reported benefit was supported by a meta-analysis of studies (n=1,079) demonstrating that cannabis use was associated with a clinically meaningful decrease in pain, on the Visual Analog Scale (8.2 vs 5.6) [35]. This obvious discrepancy likely reflects the difference between tightly controlled RCTs and broader observational data, which indicates that cannabinoids may provide subjective symptomatic relief for some patients but may not actually change core disease mechanism.

The therapeutic potential of cannabinoids for fibromyalgia is characterized by a notable divergence between satisfactory patient-reported outcomes and the low certainty of evidence from rigorous clinical trials. Observational data indicate that a significant proportion of patients report substantial reductions in core symptoms such as pain and stiffness, often perceiving cannabinoids as superior to conventional pharmacotherapies. However, systematic reviews of randomized controlled trials (RCTs), which consistently identify a high risk of bias and methodological limitations within the existing literature, do not support this perspective. These analyses suggest that the observed benefits may not stem from direct analgesic efficacy, but rather from secondary improvements in sleep quality and overall well-being. Therefore, while patient perception is overwhelmingly positive, the current evidence base is insufficient to endorse cannabinoids as a validated, evidence-based treatment for fibromyalgia, highlighting an urgent need for methodologically sound RCTs to resolve this critical evidentiary gap [36]. Moreover, the evidence is even weaker in areas like central post-stroke pain, in which a trial of nabiximols produced no clear benefit over placebo [37].

3.5 Other Pain Conditions & Psychosocial Dimensions

A recurring theme across cannabinoid studies is their impact on psychosocial factors that extend beyond direct control of symptoms. Although there is currently no high-quality evidence evaluating the efficacy of cannabinoids as a primary analgesic for conditions like migraine [38], the effect of cannabinoids on comorbid symptoms is noteworthy. In previous studies on neuropathic and chronic pain, cannabinoids were consistently associated with patient-reported improvement in sleep and anxiety [11, 36]. These findings are consistent with the supposition of a substantial therapeutic role in alleviating the global distress of chronic disease to enhance emotional and functional well-being rather than simply suppression of nociceptive signaling.

However, the evidence for cannabinoid efficacy in managing other debilitating symptoms is highly variable when moving beyond pain. For instance, despite a theoretical rationale, current evidence does not support their use in anorexia or cachexia in palliative care. A systematic review concluded that existing studies are of low quality and fail to provide convincing, unbiased evidence to justify their routine use. Although some beneficial effect on appetite was reported in previous HIV studies, it was no better than the established treatment options; therefore, their role in this indication is largely obsolete [39].

These uncertain results are in sharp contrast to the established efficacy of CBD in certain types of drug-resistant epilepsy. The systematic review of pediatric and young adult patients identified CBD as a potential adjunctive treatment, with a significant portion of patients achieving a seizure frequency reduction of 50% or more [40]. Although treatment is associated with typically mild and reversible adverse effects like drowsiness and diarrhoea, the benefits are considered to outweigh the risks in this refractory population. Further long-term analysis reveals a more nuanced picture: a 2023 meta-analysis found that while CBD's initial efficacy is stable, it may slightly decrease over time as the incidence of side effects increases. However, a notable clinical benefit is that the addition of CBD can often allow for a reduction in the dosage of concomitant anti-seizure medications, highlighting its valuable role in a broader treatment regimen [41].

he ECS is the most reasonable therapeutic target for pruritus due to its modulation of epidermal homeostasis and neurosensory signaling. The activation of CB1 and CB2 receptors in cutaneous nerve fibers and mast cells is believed to be beneficial to reduce itch due to the reduction of nerve sensitization and release of pruritogenic mediators [42]. Seminal clinical evidence supports this mechanism, with a foundational study

demonstrating that a topical cream with N-palmitoylethanolamine (PEA) significantly reduced uremic pruritus in patients undergoing hemodialysis [43]. Smaller trials suggest similar benefits in inflammatory dermatoses, such as atopic dermatitis [42].

Despite this potential, the existing evidence base is limited by the predominance of small-scale studies and the absence of standard formulations. Furthermore, the potential application in cancer-related pruritus remains theoretical and unsubstantiated by clinical data [44].

3.6 Adverse events

A systematic review and meta-analysis of 62 studies, found that compared with placebo, cannabinoid-based therapies are associated with an elevated risk of short-term adverse events (AEs). Specifically, the pooled analysis indicated a significant increase in the odds of experiencing any AE (OR 3.03; 95% CI 2.42–3.80), a serious AE (OR 1.41; 95% CI 1.04–1.92), and treatment withdrawal due to AEs (OR 2.94; 95% CI 2.18–3.96) [26].

Analysis of specific AEs identified a pronounced risk for central nervous system effects. The odds were highest for dizziness (OR 5.09; 95% CI 4.10–6.32), disorientation (OR 5.41; 95% CI 2.61–11.19), and somnolence (OR 3.83; 95% CI 2.92–5.01). Other frequently reported events included dry mouth (OR 3.50; 95% CI 2.58–4.75) and nausea (OR 2.08; 95% CI 1.63–2.65). The meta-regression also showed that elevated risk of AE was similar between cannabinoid preparations, clinical studies, and clinical indications. However, a principal limitation of this evidence base, as noted by the authors, is the complete absence of studies evaluating the long-term adverse effects of medical cannabinoid use [26].

This gap in trial data is significant, particularly when compared with the large body of evidence from observational studies on long-term, non-medical cannabis use. Convincing or converging evidence from this latter domain indicates that non-medical cannabis use is associated with poor mental health and cognition, an increased risk of motor vehicle accidents, and, if used during pregnancy, detrimental effects on offspring. Consequently, guidelines strongly advise against cannabis use in adolescents and young people — when most mental health disorders have their onset, and cognition is paramount for optimizing academic performance — as well as in pregnant women and drivers [45].

Although most of this concern relates to younger and middle-aged populations, understanding the safety and prevalence of cannabis use among older adults remains challenging. A large cross-sectional study from 2025 involving 4503 older US veterans aged 65 to 84 highlights this issue. Cannabis use in this group is common — 10.3% reported using cannabis at least once in the past 30 days, nearly double the 5.2% reported in the U. S. general population in 2022. Past-year use among these veterans (14.1%) exceeds that of civilians (8.4%). The main reasons for medical use were pain management (56 4%), mental health concerns (18.4%), and sleep issues (16.0%). A key safety concern is the high rate of Cannabis Use Disorder (CUD); among veterans who used cannabis in the past 30 days, 36.3% met the criteria for CUD, which the authors found to be “concerning” and at the “higher end” compared to other cannabis- using populations. The risk increases with frequency; over half of recent users (52. 4%) reported using cannabis on 20 days or more in the previous month. The form of administration also matters: past 30-day inhaled cannabis use (smoking or vaping) was linked to 3.56 times higher odds of CUD compared to using edibles alone. These findings, along with others mentioned by the authors, point to the need for routine clinical screening of at-risk older adults, especially those with anxiety or difficulties in daily activities, which are linked to a higher CUD risk [46]. There is also significant evidence linking cannabis use to other psychiatric risks, particularly the development of psychotic disorders. A systematic review and meta-analysis examined the dose-response relationship between cannabis use and psychosis. Analyzing 10 studies with a total of 66,816 participants, it confirmed a strong, dose-dependent association: the largest cannabis users had a pooled odds ratio (OR) of 3.90 (95% CI 2.84–5.34) for schizophrenia or other psychosis- related outcomes, compared to nonusers. The median “average” cannabis user had about twice the risk (OR 1.97). This association was consistent across study designs and outcome measures, leading the authors to conclude that high cannabis use is a significant risk factor for psychosis, although no clear causal mechanism has been identified [47].

3.7 Opioids vs Cannabinoids

A recent network meta-analysis suggests that cannabinoids may have a similar, albeit modest, therapeutic efficacy to opioids for chronic non-cancer pain due to having a more favorable safety and tolerability profile; these findings contradict the existing analgesic hierarchy. The analysis, which consisted of 90 trials and >22,000 patients, found low to moderate certainty evidence that medical cannabis and opioids did not have clinically significant differences on key outcomes, including pain relief (WMD 0.23 cm on a 10 cm VAS), physical functioning, and sleep quality. Neither agent demonstrated superiority over placebo in improving role, social, or emotional functioning. However, safety and tolerability were an important and less well-established difference, and moderate certainty evidence showed that patients who were treated with medical cannabis had a significantly lower rate of stopping treatment for the presence of an adverse event than individuals prescribed opioids (OR 0.55, 95% CI 0.36 to 0.83). Crucially, this safety advantage is most pronounced when considering the fundamental risk of fatal overdose. Unlike opioids, which directly suppress respiration by acting on receptors in the brainstem, cannabinoids lack this mechanism, making a lethal overdose from their use virtually impossible. This neurobiological distinction is the primary basis for their superior safety. Collectively, these findings suggest that while the analgesic effect of cannabinoids is similar to that of opioids, their superior safety and tolerability profile position them as a viable alternative in the management of chronic non-cancer pain [48].

Furthermore, the different addiction risk profiles experienced by opioids and cannabinoids are large and are one of the most important differences between the two types. Opioids have a very high dependence liability, attributed to the fact that they are highly potent agonists of mu-opioid receptors, which induce extreme euphoria and potent reinforcement of drug-taking behaviour [49]. This neurobiological process drives the rapid emergence of tolerance and the severe, medically significant physical withdrawal syndrome with severe pain, nausea and vomiting, and autonomic impairment, which strongly induces continued use to escape the symptoms [50]. Unlike chronic cannabis use, which can result in CUD, the general risk of dependency on cannabis is much lower. The cannabis withdrawal syndrome is established, comprising less life-threatening chronic symptoms, such as irritability, anxiety, poor sleep, and decreased appetite, that are significantly milder than the opioid withdrawal syndrome [51]. This fundamental difference in dependence liability and withdrawal severity underscores the significantly greater public health risk associated with opioid use compared to cannabinoids.

These significant safety concerns and the modest efficacy of single-agent therapies have fueled growing interest in adjuvant analgesics and multimodal therapy, where different medications are combined to achieve synergistic effects, improve pain relief, and reduce the required doses of conventional analgesics, thereby minimizing their adverse effects. In this context, cannabinoids are being investigated not only as alternatives but also as effective adjuvant agents. For instance, a systematic review and meta-analysis found that the addition of cannabinoids to existing opioid therapy was associated with a significant reduction in opioid dosage, indicating an "opioid-sparing" effect [52]. This suggests that integrating cannabinoids into pain management regimens could not only enhance analgesic efficacy but also mitigate the risks associated with high-dose opioid therapy.

4. Conclusions

The evidence shows that cannabinoids work best for specific medical conditions. Nabiximols stands as an approved treatment for MS-related spasticity based on strong evidence [26, 29] while CBMs show moderate effectiveness for treating neuropathic pain according to 2024 guidelines [14]. The Cochrane reviews demonstrate that cannabinoids fail to provide any benefit for cancer pain management [17]. For inflammatory conditions, such as rheumatoid arthritis and fibromyalgia, the data are inconclusive and insufficient for recommendations, despite positive patient reports [33, 36].

The safety profile of cannabinoids includes common mild to moderate short-term side effects, which include dizziness and drowsiness [26], but they differ from opioids because they do not cause fatal respiratory depression and have lower addiction potential [48, 51]. Evidence also supports an "opioid-sparing" effect, positioning cannabinoids as a potential adjunctive therapy [52]. Evidence also highlights specific risks, such as a higher susceptibility to cannabis use disorder among older adults [46] and an increased risk of psychosis associated with high-dose use [47]. All clinical trials lack essential long-term safety information, which represents a main limitation of the current evidence base [26].

Overall, cannabinoids should be considered as an adjunctive therapy rather than a first-line therapy, reserved for carefully selected patients who do not achieve sufficient relief with standard treatments. Future progress requires large-scale, randomized controlled trials; standardized formulations; long-term safety evaluations and international regulations to define the precise role of cannabinoids in evidence-based pain care.

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