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DISCOVERY SCIENTIFIC SOCIETY

The efficacy and safety of medical cannabis in the management of chronic pain: A systematic review

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ABSTRACT

Chronic pain is a worldwide health issue that over 20% of word's population suffer from and it requires evidence-based treatment approaches. Chronic pain remains an unexplained condition that might be caused by biological, psychological and social factors. Managing it effectively is essential for improving the patients' ability to perform daily activities, enjoy life and maintain independence. It could also mean reducing long-term healthcare costs. Alongside conventional approaches to chronic pain treatment, medical cannabis has become a subject of growing international interest and scientific investigation. The study aimed to assess the safety of medical cannabis as a novel approach to chronic pain treatment.

Keywords: chronic pain, pain management, medical cannabis, analgesia

1. INTRODUCTION

Chronic pain represents a growing global public health priority, often associated with significant emotional distress and functional disability. It negatively affects patients' quality of life and functional capacity. Therefore, delivering appropriate care for patients with chronic pain is a significant challenge for healthcare providers. The pathogenesis is complex and multifactorial, involving biological, psychological and social factors. Beyond the physiological processes of pain perception (Gatchel et al., 2007), the experience of chronic pain also involves thoughts, feelings and behaviors, as well as the social environment such as family and support system (Kovačević et al., 2024).

Over the past few decades, the understanding of chronic pain has increased significantly. A notable development is the introduction of a new classification in the 11th revision of the International Classification of Diseases (ICD-11), which distinguishes between chronic primary and chronic secondary pain (Nicholas et al., 2019; Korwisi et al., 2021).

In recent years, the growing interest in improving the quality of life and reducing the use of opioid treatment has started a new wave in research focused on discovering an optimal therapy. One example of a modern approach to chronic pain management is the use of medical cannabis. In this review, we provided an analysis

of relevant literature covering the subject of the significance of medical cannabis as a part of novel pain treatment.

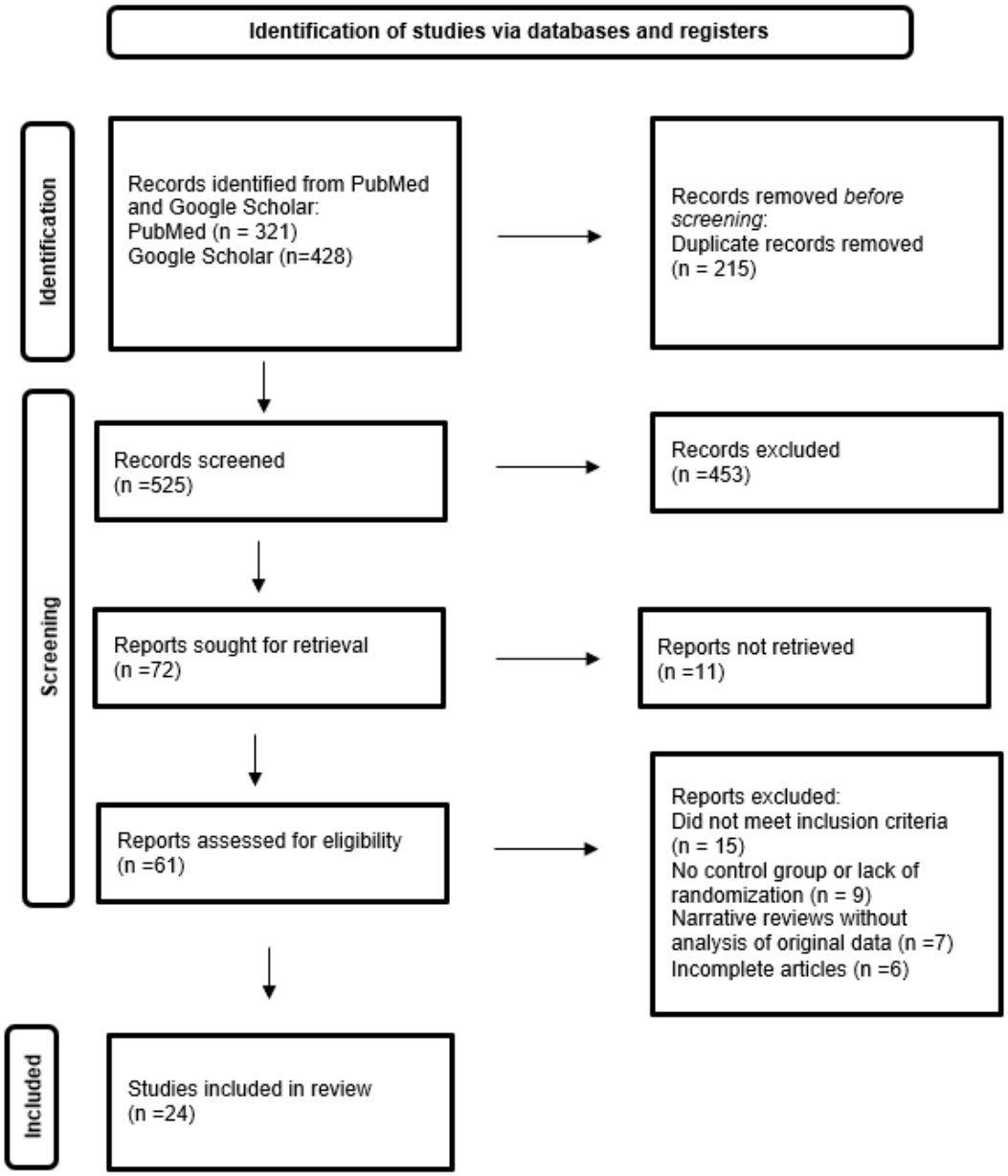

Figure 1 Flow chart

2. REVIEW METHODS

We reviewed studies from major scientific databases, such as PubMed and Google Scholar, focusing on chronic pain treatment by medical cannabis. These selected articles were analyzed and summarized in this review. We used keywords such as medical cannabis, cannabinoids, THC, CBD, chronic pain, neuropathic pain, cancer pain, musculoskeletal pain, pain management, and analgesic effect to search in these databases. We set the time range of published articles to 2011-2024 and included some older publications if we considered them valuable for understanding the issue. All publications used in this review were written in English.

The primary reason for the bias in this study may be the limited number of participants. A smaller sample size might not be sufficiently representative. The limited number of publications in the problem area and the absence of randomization in some included studies are other sources of bias (figure 1).

3. RESULTS

Classification and Pathophysiology of Chronic Pain

The cause of chronic pain is heterogeneous, as many different factors can contribute to its development. According to the most widely accepted model—the biopsychosocial model - beyond the physical sensation, chronic pain is a condition caused by variety of factors, such as biological, psychological and social ones (Nicholas et al., 2019; Korwisi et al., 2021; Kovačević et al., 2024; Park & Moon, 2010; Gatchel et al., 2007). The foundation of pain sensation lies in biological factors, including processes of pain perception (Gatchel et al., 2007). On the other hand, pain experience is also caused by psychological factors such as thoughts, feelings and behaviors. Social factors include patients' social environment, such as family and social support systems. (Kovačević et al., 2024).

The International Classification of Diseases (ICD-11) divides chronic pain into chronic primary pain (CPP) and chronic secondary pain (CSP) (Nicholas et al., 2019; Korwisi et al., 2021). According to the ICD-11 classification, chronic primary pain last longer than 3 months and is associated with emotional suffering and physical dysfunction, while it cannot be explained by another condition. Psychological, biological, and social factors all contribute and cause chronic pain, considered as a condition on its right. On the other hand, chronic secondary pain is the pain that originally developed as a symptom of another disorder or disease process (Nicholas et al., 2019; Korwisi et al., 2021). However, chronic secondary pain, although symptomatic of an underlying condition, often requires specialized, interdisciplinary pain management (Table 1).

Table 1. Classification and Pathophysiology of Chronic Pain

Type	Definition	Examples
Chronic Primary Pain	Pain lasting >3 months not better explained by another condition; includes biopsychosocial factors	Fibromyalgia, nonspecific low back pain
Chronic Secondary Pain	Pain resulting from an identifiable underlying condition	Cancer pain, post-surgical pain, arthritis

The Endocannabinoid System and Pain Pathways

The endocannabinoid system (ECS) is a neurotransmitter system, distributed throughout the brain and body, involved in pain perception (Atakan, 2012). The analgesic effects of cannabinoids are primarily centered around the activation of two key receptors such as cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R) (Shehata et al., 2022; Narouze, 2021).

The distribution of these receptors is distinct but complementary in pain modulation. CB1R is predominantly found in the central and peripheral nervous systems. These receptors are located along both descending and ascending pain pathways, from peripheral neuronal terminals to the supraspinal regions. The location of CB1R includes the dorsal root ganglion, which is a key relay station for the pain neuronal circuit (Gottschling et al., 2020). High concentration of CB1 receptor is also found in areas involved in pain modulation within the central nervous system, such as the ventral posterolateral nucleus of the thalamus, the periaqueductal gray matter of the midbrain, the nucleus tractus solitarius, and the dorsal horn of the spinal cord. While predominantly neuronal, small amounts of CB1 receptors are also found in peripheral tissues such as the heart, liver, pancreas, muscle, adipose tissue, and the reproductive system. Due to limited amounts of CB1 receptors in the brain stem, their impact on the respiratory center is much milder than opioids (Safi et al., 2024; Gottschling et al., 2020).

In contrast, the CB2 receptor is strongly recognized as both a peripheral and central cannabinoid receptor (Shehata et al., 2022). Although primarily expressed in peripheral tissues and immune cells, where they play a role in inflammation and immunomodulation, the CB2 receptor is also located within the nervous system in pain-related areas (Gottschling et al., 2020; Cortez-Resendiz et al., 2025; Starowicz and Finn, 2017). These areas include the cerebral cortex, hippocampus, striatum, amygdala, and thalamic nuclei (Shehata et al., 2022). Both CB1 and CB2 receptors are also located in the gastrointestinal tract, where they can affect the microbiome. They are taking part in the regulation of their motility and immunological processes (Safi et al., 2025).

The endocannabinoid system includes endogenous cannabinoid ligands. Two of the best-known endocannabinoid molecules are N-arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG). Endocannabinoids are released on demand at postsynaptic terminals and travel retrogradely to activate cannabinoid CB1 and CB2 receptors located on presynaptic terminals (Starowicz and Finn, 2017).

A fundamental mechanism by which different cannabinoid receptors perform their analgesic effect is through modulation of pain impulse transmission by modifying the release of neurotransmitters at the synaptic cleft. Both CB1R and CB2R are members of the G protein-coupled receptor (GPCR) family that are sensitive to pertussis toxin (PTX)-sensitive Gi/o proteins. Upon activation, this protein inhibits the activity of adenylate cyclase, subsequently decreasing the production of cyclic AMP (Shehata et al., 2022; Narouze, 2020). This mechanism activates specific G protein-dependet potassium channels while inhibiting voltage-gated sodium channels, leading to neuronal hyperpolarization. As a result, hyperpolarization suppresses the electrical conduction and inhibit synaptic transmission (Narouze, 2020). This results in a reduction in the release of neurotransmitters, which lowers pain transmission and perception (Safi et al., 2025).

Cannabinoids induce an analgesic response, particularly in hyperalgesia, neuropathic pain, and inflammation (Narouze, 2020; Safi et al., 2025). The mechanism of suppressing inflammation may be attributed to reduced production of inflammatory cytokines, inhibition of inflammation-related enzymes, and even the induction of apoptosis in inflammatory cells (Shehata et al., 2022). Cannabinoid–opioid cross-modulation and synergistic interactions significantly enhance the antinociceptive effects of cannabinoids (Narouze, 2020). Through close interaction between the cannabinoid and opioid signaling pathways, a synergistic mechanism of action is observed with the analgesic effect of THC, aiding in altering pain experience (Safi et al., 2025).

Overall, the endocannabinoid system might be an essential modulator of pain pathways. Discovering its receptors and interactions began a discussion of using cannabinoid-based medicines for pain management (Table 2).

Table 2. Mechanisms of Action of Cannabinoids in Pain Modulation

Receptor / Component	**Primary Location**	**Mechanism of Action**	**Role in Analgesia**
CB1 receptor	Descending and ascending pain pathways (e.g. the dorsal root ganglion, the ventral posterolateral nucleus of the thalamus, periaqueductal gray matter of the midbrain, nucleus tractus solitarius, the dorsal horn of the spinal cord)	CB1 activation -> adenylate cyclase activity inhibition -> cyclic AMP production decrease -> potassium channels activation and voltage-gated sodium channels inhibition -> neuronal hyper-polarization -> neurotransmitter release reduction	Suppresses pain signal transmission
CB2 receptor	Immune cells, peripheral tissues, and CNS (e.g. cerebral cortex, hippocampus, striatum, amygdala, thalamic nuclei)	Reduction in the production of inflammatory cytokines, inhibition of inflammation-related enzymes, induction of apoptosis in inflammatory cells	Suppresses pain signal transmission, suppressing inflammation
ECS – endokannabinoides (AEA, 2-AG)	Released on demand from postsynaptic terminals	Retrograde signaling to presynaptic CB1/CB2 receptors	Provides broad regulatory control over nociceptive processing

Efficacy of Medical Cannabis in Pain Management

Pain intensity is a critical patient-reported outcome in clinical trials evaluating analgesic interventions for chronic pain. There are a variety of scales that are used to measure pain intensity, including the Visual Analog Scale (VAS), typically ranging from 0 to 100 mm, and the Numerical Rating Scale (NRS), typically ranging from 0 to 10. These tools are widely employed to quantify subjective pain level. The review identified several Randomized Controlled Trials (RCTs) and systematic reviews and summarized the potential effectiveness of cannabis-based medicines for chronic pain, including neuropathic, cancer and musculoskeletal pain.

A systematic review and meta-analysis conducted by Whiting et al. examined the use of Nabiximols in chronic pain management. Nabiximols is an oromucosal spray containing a standardized dose of 2.7 mg of delta-9-tetrahydrocannabinol (THC) and 2.5 mg of

cannabidiol (CBD) in each spray (Longo et al., 2021). Nabiximols administration was associated with a greater average reduction in pain assessment scores on a 0-10 Numerical Rating Scale (NRS) compared with placebo (Whiting et al., 2015). The weighted mean difference (WMD) from 6 trials was −0.46 (95% CI, −0.80 to −0.11). The same meta-analysis also stated that patients using nabiximols were more likely to to report an improvement (OR, 2.08 [95% CI, 1.21 to 3.59]; 6 trials) compared with placebo (Whiting et al., 2015).

One large randomized controlled trial conducted by Nugent et al., involving 246 patients with peripheral neuropathic pain using nabiximols, found that those who completed the study and responded positively had a significant decrease in pain (odds ratio, 1.97 [CI, 1.05 to 3.70]). However, when including all participants in that study, even those who did not response to the intervention, the reduction in the NRS pain score did was not clinically or statistically significant (Nugent et al., 2017). Studies evaluating nabiximols for chronic pain reported statistically important pain levels decreases and an increased likelihood of response compared to placebo, based on multiple trials. The reviewed studies varied in sample size, duration (typically 2 to 3 weeks), and study design. Long-term outcomes were generally not reported.

A Cochrane systematic review executed by Mücke et al., (2018) specifically examining cannabis-based medicines for chronic neuropathic pain included 14 studies. The study found that these treatments were more effective than placebo in the reducing mean pain intensity, achieving 50% or greater pain relief. The pooled analysis showed a standardized mean difference (SMD) of −0.35 (95% CI −0.60 to −0.09), with a P value of 0.008. A systematic review carried out by Tsai et al., (2022) concluded that cannabinoids din not provide better results than other commonly prescribed drugs for central neuropathic pain. A randomized trial conducted by Nugent et al., (2017) involved 55 participants with HIV-associated neuropathic pain. They were randomly chosen to smoke either 3.56% THC cigarettes or a placebo three times per day. Among patients who completed the study, 52% in the 3.56% THC group reported improvement regarding pain control compared with 24% in the placebo group. The study had a short duration of five days.

A randomized, double-anonymized, single-session, placebo-controlled crossover study conducted by Wallace et al., (2015) in 16 patients with painful diabetic peripheral neuropathy assessed the effects of inhaled vaporized cannabis (VOLCANO-System-Vaporizer). Vaporized cannabis used in the study contained varying THC concentrations: low (1% THC), medium (4% THC), and high (7% THC) compared to placebo. The study found a significant difference in spontaneous pain scores between doses ($p<0.001$). Specifically, there were substantial comparisons between the placebo and the low, medium, and high doses. Higher doses (7% THC) were associated with impaired performance on two of three neuropsychological tests. Higher doses (7% THC) were associated with impaired performance on two of three neuropsychological tests (Wallace et al., 2015).

A comprehensive review conducted by Häuser et al., (2023) included five randomized controlled trials assessing oromucosal nabiximols or THC alone with 1539 patients suffering from moderate or severe cancer pain despite receiving opioid therapy. The results of the study indicated that 31.9% in the nabiximols group reported being much or very much improved, compared to 23.0% in the placebo group (RD 0.06, 95% CI 0.01 to 0.12; P = 0.03). Additionally, one trial used cannabidiol (CBD) in specialist palliative care. The results were not in favor of medical cannabis, mostly because no pain alleviation was observed in patients with advanced cancer. A separate review by the American Society of Pain and Neuroscience examined three large randomized controlled trials on the use of cannabinoids in patients with cancer suffering from chronic pain. Once again, the results did not support the idea of using cannabis-based medicines daily. Although the trials endorsed the concept, the findings were given a grade D recommendation due to limited confidence (Strand et al., 2023).

A survey performed by Mangual-Pérez et al., (2022) assessed analgesic effects in 184 patients with musculoskeletal pain. Patients were asked to rate their pain intensity on Numerical Rating Scale (NRS). It decreased from 7.43 to 3.41 after using cannabis-based treatment methos (mean reduction: 4.02 points; P < 0.001). An observational cohort study by Cottrell et al., (2024) investigated 61 new users of medical cannabis with playing-related musculoskeletal disorders (PRMD). The mean pain intensity score decreased from 14.41 ± 8.56 at baseline to 11.80 ± 9.00 at six months (P = 0.006). The change in pain score at six months differed significantly between new users (−2.61 ± 7.15) and long-term users (0.83 ± 0.79) (P = 0.023). Pain interference, measured by the MPIIQM50 scale, also showed statistically significant reductions across all groups at six months among new users

(P = 0.002). Another survey by Johal et al., (2020) included approximately 1000 participants, two-thirds of whom reported chronic musculoskeletal pain. Among these, 75% indicated experiencing symptom relief after receiving a cannabis prescription. From nearly 2600 qualitative responses collected, over one-third described health benefits associated with medical cannabis use.

Side Effects of Medical Cannabis

Reported side effects associated with medical cannabis use represent a variety of different results, from frequently noted mild effects to less common, severe occurrences. The administration of cannabis-based medicines is associated with a higher risk for short-term adverse effects (Whiting et al., 2015). Common adverse effects include weakness, lightheadedness, confusion, disorientation, euphoria, and drowsiness. Another group of side effects were physical symptoms that include diarrhea, dry mouth, nausea, and vomiting (Whiting et al., 2015). Sleepiness, dizziness, and mental problems such as confusion were reported more frequently in groups receiving cannabis-based interventions than in placebo groups (Mücke et al., 2018). A study involving patients with musculoskeletal pain reported self-reported side effects such as dry mouth (43%), fatigue (23%), and lack of motivation (15%). In this group, 39% reported no cannabis-related side effects (Leroux et al., 2024).

While most reported adverse events were mild, instances of major side effects such as suicide attempts, paranoia, and agitation have been reported (Nugent et al., 2017). In one pooled analysis, 80.2% of patients receiving cannabis-based medicines experienced at least one adverse event, compared to 65.6% in the placebo group (number needed to treat for harm [NNTH]: 5) (Mücke et al., 2019). Nervous system disorders occurred in 61.1% of patients in the cannabis group and 28.7% in the placebo group (NNTH: 3). Psychiatric disorders were reported in 16.5% and 4.9% of patients, respectively (NNTH: 10). The number of patients who stopped medical cannabis treatment due to side effects was 10.4% in the cannabis group versus 4.7% in the placebo group (NNTH: 25) (Mücke et al., 2019). Long-term safety data were not described in the included studies, as higher-quality research is still needed (Table 3 & 4).

Table 3. Reported Adverse Effects of Medical Cannabis Use

Adverse Effect	Raported Frequency (%)	Source
Dry mouth	43%	Leroux et al., 2024
Fatigue	23%	Leroux et al., 2024
Lack of motivation	15%	Leroux et al., 2024
Dizziness, drowsiness, nausea	-	Longo et al., 2021; Häuser et al., 2023
Psychiatric symptoms	16.5%	Häuser et al., 2023
Serious events (e.g. paranoia, suicide attempts)	Rare	Tsai et al., 2022

Table 4. Risk of Adverse Events in Cannabis vs. Placebo Groups

Adverse Outcome	Cannabis Group	Placebo Group	NNTH	Source
Any adverse event	80.2%	65.6%	5	Häuser et al., 2023
Nervous system disorders	61.1%	28.7%	3	Häuser et al., 2023
Psychiatric disorders	16.5%	4.9%	10	Häuser et al., 2023
Withdrawal due to adverse events	10.4%	4.7%	25	Häuser et al., 2023

4. DISCUSSION

In this review, we tried to assess the safety of medical cannabis and its potential success in the treatment of chronic pain, including neuropathic, musculoskeletal, and cancer-related pain. The findings support the possible role of medical cannabis as a moderately effective treatment for chronic pain in specific patient populations. However, the clinical relevance of these effects remains limited and inconsistent across studies.

Gathered evidence from various randomized controlled trials (RCTs) and meta-analyses indicates that cannabis-based formulations such as nabiximols and inhaled THC may be associated with small pain relief scores in patients with neuropathic pain. Some studies also report improved global impression scores. However, findings across studies are not entirely consistent and the overall quality of the evidence has limitations, including variations in study design and risk of bias, small sample sizes in many trials, and few studies reporting outcomes beyond 2 to 3 weeks, with none reporting long-term outcomes in one review. These factors prevent us from making firm opinions about the potential success of long-term cannabis-based treatment.

Outcomes of the surveys completed by patients suffering from musculoskeletal pain suggest pain reduction after cannabis use. These data mean positive feedback from patients; however, they are limited due to recall bias, lack of blinding, and placebo effects.

Controlled trials in this area remain limited, and often report only small effect sizes that do not consistently reach the minimal clinically important difference thresholds.

In contrast, evidence regarding the use of cannabinoids in cancer-related pain is less supportive. Meta-analyses including patients with opioid-refractory cancer pain did not demonstrate clinically meaningful improvements with nabiximols or THC compared to placebo. Trials assessing nabilone, synthetic THC analogues, and cannabidiol (CBD) also failed to show significant pain reduction in oncology chronic pain. The American Society of Pain and Neuroscience assigned a grade D recommendation for cannabis in cancer pain, reflecting limited confidence in current evidence.

Due to the risks, including short-term adverse effects, cannabis use requires careful administration and regular clinical monitoring. Notably, serious side effects were rare. We advise a cautious and conservative approach to the medical use of cannabis. The interpretation of results is limited by significant variation in study design, dosage, and the methods used by authors to measure the results. Moreover, most studies were short-term, making it difficult to assess long-term efficacy or safety. Future high-quality RCTs with longer follow-up periods, standardized cannabinoid formulations and consistent methods for measuring pain relief are needed to provide more substantial evidence.

The safety profile of medical cannabis shows a higher probability of short-term adverse side effects compared to placebo. Long-term safety data is limited, and further research is necessary to assess the risk profile over more extended periods of use. Clinicians should consider medical cannabis with caution in the management of chronic pain due to limited long-term data. In patients who have not responded well to conventional therapies—particularly for neuropathic and musculoskeletal pain—cannabis-based interventions may be an option under close clinical supervision. However, high-certainty evidence does not support routine prescription.

5. CONCLUSION

Medical cannabis may offer modest pain relief in select patients with chronic neuropathic or musculoskeletal pain, but its effectiveness is not supported in cancer-related pain. The overall quality of evidence is moderate to low, and adverse effects are more likely to occur with cannabis-based medicines than with a placebo. We should focus on higher-quality research, prioritizing standardized dosages and clearly defined outcome measures. Until better evidence becomes available, clinicians should consider the potential benefits of cannabis-based medicines while still having risks in mind. They ought to consider patient preferences while making treatment decisions.

Author's Contributions

Paulina Wasilewska: Conceptualization, literature search, manuscript drafting, and correspondence.
Paula Klemenska: Data analysis and synthesis, writing – review and editing.
Weronika Pierudzka: Literature review, table preparation.
Józef Sławatycki: Critical revision of the manuscript, data curation
Konrad Warczak: Supervision, methodological guidance, final approval of the version to be published.

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Informed consent

Not applicable.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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