
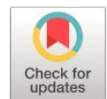


# Medicinal Cannabis (MC) and Cannabis-Based Medicines (CbMs) for Acute and Chronic Pain Treatment: A Review Article

*Cannabis medicinal (MC) y medicamentos a base de cannabis (CBM) para el tratamiento del dolor agudo y crónico: un artículo de revisión*

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**Palabras claves:**

Cannabis Medicinal (MC), Cannabidiol (CBD), Medicamentos a Base de Cannabis (CBM),  $\Delta 9$  - tetrahydrocannabinol (THC), Dolor crónico, cannabinoides.

**Keywords:**

Medicinal Cannabis (MC), Cannabidiol (CBD), Cannabis-Based Medicines (CBM),  $\Delta 9$  - tetrahydrocannabinol (THC), Chronic Pain, cannabinoids.

**Resumen**

**Introducción:** Cannabis ha sido vastamente usado con fines medicinales por siglos debido a sus propiedades analgésicas. Evidencia científica sugiere que el cannabis medicinal posee un gran potencial para el tratamiento del dolor agudo y crónico. Sin embargo, los resultados han sido inconsistentes.

**Objetivos:** Hacer una revisión sobre la eficacia del cannabis medicinal y de los medicamentos a base de cannabis para el tratamiento del dolor agudo y crónico de cualquier origen.

**Metodología:** Google Scholar y PubMed fueron usados para encontrar ensayos clínicos aleatorizados, doble ciego, y controlados con placebo de casos de dolor agudo y crónico.

**Resultados:** Solo cuatro de los once ensayos clínicos que formaron parte de este artículo de revisión encontraron beneficios del tratamiento a base de cannabis para reducir el dolor crónico. Mientras que siete ensayos clínicos revelaron que el cannabis medicinal y los medicamentos a base de cannabis no tienen una mayor eficacia que el tratamiento de placebo. **Conclusiones:** El cannabis medicinal y los medicamentos a base de cannabis podrían ser de gran ayuda como medicina complementaria.

**Area de estudio general:** Medicina

**Area de estudio específica:** Algesiología

**Abstract**

**Introduction:** Cannabis has been used for medicinal purposes for centuries due to its analgesic properties. Some evidence suggests that cannabis has an enormous potential for acute and chronic pain management. However, the results have been inconsistent.

**Objectives:** To review the quality of the data gathered over the years about medicinal cannabis and cannabis-based medicines to discover the analgesic efficacy of using cannabis for acute and chronic pain.

**Methodology:** Google Scholar and PubMed were used to find randomized, double-blinded, placebo-controlled reports of acute and chronic pain cases of any origin. **Results:** Only four out of eleven studies that took part in this review found some beneficial outcomes of the cannabis treatment. Seven studies revealed that medicinal cannabis and cannabis-based medicines were no better than the placebo treatment.

**Conclusions:** Medicinal cannabis and cannabis-based

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medicines may be useful when used as an adjunctive medicine.

**General area of study:** Medicine

**Specific area of study:** Algesiology

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## Introduction

Despite its wide variety of practical uses in different fields, cannabis production and manipulation have been themes of considerable controversy for many decades. According to Crocq (2022), it has been estimated that the use of cannabis dates around 11,700 years ago. The plant itself seems to be originated from Central Asia (Afghanistan, Mongolia, Pakistan) where it was domesticated to produce strains which were later used either as fibers or as a psychotropic drug. Then, it was spread all over Europe and Asia by nomadic people. Furthermore, it has been argued that cannabis was anciently used as a medicinal herb to treat loss of appetite, sleeping disorders, anxiety, diverse types of pain and nausea in some countries, such as India, China, Egypt, and Greece (Crocq, 2022). Despite its popularity in other Asian countries, it was not until the late 19<sup>th</sup> and early 20<sup>th</sup> century when cannabis became popular in Western countries. Crocq (2022) argues that Empress Elisabeth of Austria and Queen Victoria consumed cannabis to treat menstrual cramps, increase appetite and relieve cough. However, cannabis eventually became a subject of stigmatization in many Western countries in the mid-20<sup>th</sup> century (Rull, 2022). As many restrictions were introduced in the US; the Marihuana Tax Act was passed to regulate the use and possession of cannabis in 1937. Therefore, cannabis was later removed from the US Pharmacopeia (Savage et al., 2016). Yet, some people argue that the decision to make cannabis illegal in the US seems to be based on racist beliefs. Smith et al. (2022) indicates that cannabis was commonly associated with the African American and Hispanic communities in 1923. Therefore, the stigmatization and later illegalization of cannabis led to a misconception of the plant's properties and a lack of research opportunities. As a result, the medicinal properties of cannabis remained unknown for many years. Nevertheless, researchers' fascination about the therapeutic properties of the plant persisted over time. Due to its enormous pharmaceutical potential, cannabis has undergone a process of destigmatization in recent years. The legalization of cannabis production in the US, Canada and some European countries has increased the interest of conducting research and finding new industrial and medicinal applications. Recent evidence suggests that cannabis-based medicines may be effective in reducing pain and alleviating symptoms of patients who suffer from insomnia, epilepsy, multiple sclerosis (MS) and cancer (Kleckner et al., 2019). The first prescription drug derived from cannabis was approved by the US Food and Drug Administration (FDA) in 2018. Epidyolex

became the first ever commercially available cannabis-based medicine, and its main function is to treat epilepsy (MacCallum & Russo, 2018). Nowadays, the most common prescribed cannabis-based medicines are: Nabiximols (Sativex), Nabilone and Epidyolex. Nabilone is commonly used to treat the side effects of chemotherapy, whereas Nabiximols is often used for the treatment of multiple sclerosis (MS). Even though cannabis is legal for medicinal and recreational purposes in some states in the US, it is still listed as a Schedule I drug by the Food and Drug Administration (FDA) for its capability to cause intoxication and abuse. On the other hand, researchers have been able to make some important discoveries about cannabis. It has been determined that cannabis consists of two main subspecies: *C. sativa* and *C. indica*. The difference between these two principal taxonomic groups is in their geographical origins. *C. sativa* originates from India, whereas *C. indica* had origins in Afghanistan (McPartland & Small, 2020). Furthermore, years of arduous research has led us to the findings of two crucial components of cannabis: the endocannabinoid system (ECS) and cannabinoids. The endocannabinoid system (ECS) consists of receptors that can be found in our body, particularly in our brain. The main purpose of the ECS is to regulate the brain's cognitive and behavioral functions. While cannabinoids are active biochemical substances which can bind to the cannabinoid receptors of the brain (Fisher et al., 2021). When cannabinoids reach the endocannabinoid system, they could alter our behavior (Young & Denovan-Wright, 2022). In addition, it has been discovered that cannabis contains more than 120 cannabinoid compounds. Navarro et al. (2022) states that two of the most bioactive compounds are  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD). Although THC and CBD are both found in the cannabis plant, they have different chemical structures and properties. THC is often attributed all the psychoactive properties (Stella, 2023). It is believed that CBD and THC might be beneficial for the treatment of acute and chronic pain. Chronic pain is a condition which can cause enduring physical pain and disability and could last more than 3 months. It is estimated that 20% of the population around the world are affected by chronic pain (Dyukukha et al., 2021). Despite the growing evidence about the therapeutic properties and health benefits of medicinal cannabis and cannabis-based medicines for acute and chronic pain management, there seems to be some inconsistencies in those findings and some scientists claim that cannabis-based medicines do not improve a patient's overall wellbeing. For this reason, it is especially important to critically analyse the existing literature and evaluate the effectiveness of medicinal cannabis and cannabis-based medicines. In this review, the advantages, and disadvantages of using cannabis-based medicines and medicinal cannabis to treat acute and chronic pain will be discussed. The principal objective of this research is to evaluate the veracity and quality of existing findings and try to discover whether cannabis-based medicines and medicinal cannabis could be beneficial for patients who suffer from acute and chronic pain or not.

### Materials and method

Google Scholar and PubMed were used to find double-blind, randomized, placebo-controlled clinical trials of medicinal cannabis and cannabis-based medicines for the treatment of acute and chronic pain of any origin. Due to the extremely limited research data, I decided to expand the range of time of the randomized trials publications since its inception until 2023. I summarized data concerning the type of delivery method (oral, smoking and vaporization) delivery options, number of participants, age, gender, comorbidities, duration of the clinical trial, type of intervention, dosing, outcomes, health benefits and adverse effects of the treatment. I excluded review articles and other secondary papers. I only selected reports written in English. I used the following keywords: “double-blind,” “randomized,” “placebo-controlled clinical trials,” “chronic pain,” “cannabis,” “cannabinoids,” “cannabis-based medicines” to find the eligible clinical reports. I only selected 11 reports out of many articles. I excluded cannabis-dependent patients’ cases. I focused only on cannabis-based medicines and medicinal cannabis products to treat pain-inducing diseases of any origin.

### Results

**Table 1**

*Summary of the patient demographics in the selected case studies*

Reference	Number of Patients(n)	Country Of origin:	Gender	Mean age (years)	Comorbidities:	Pain Diagnosis:	Previous Cannabinoids Use:	Amount of Cannabis use per month (g)	mean BMI (Kg/m2)	Concurrent Medications:
Chaves et al. 2020	17	Brazil	All Female	51.9	Depression and Anxiety	Chronic musculoskeletal pain	No	None	Unknown	Antidepressants, benzodiazepines, opioids
Almog et al. 2020	27	Israel	19 Male and 8 Female	48.3	Diabetes	Chronic pain, phantom/stump pain, diabetic neuropathy	Yes	16-30	27.8	Antidepressants, benzodiazepines, anticonvulsants, analgesics, opioids
Abrams et al. 2020	23	USA	10 Male and 13 Female	37.6	Unknown	Chronic pain with acute vaso-occlusive crisis	Yes	Unknown	Unknown	Analgesics, Opioids
Van de Donk et al. 2019	20	Netherlands	All Female	39.13	None	Chronic Pain	No	None	29.7	Paracetamol and Ibuprofen
Selvarajah et al. 2010	30	United Kingdom	19 male and 11 female	58.2	Depression	Chronic painful DPN	Yes	Unknown	31.9	Antidepressants
Narang et al. 2023	90	USA	35 Male and 55 Female	61	Kidney/ureteral stones	Post-Ureteroscopy pain	No	None	28	Oxycodone, tamsulosin, oxybutynin, phenazopyridine
Ware et al. 2010	21	Canada	9 Male and 12 female	45.4	Allodynia, hyperalgesia	Chronic neuropathic pain	No	None	Unknown	Antidepressants, anticonvulsants, Anesthetics, opioids
Turcotte et al. 2015	15	Canada	2 Male and 13 female	45.5	None	Chronic neuropathic pain	No	None	Unknown	Gabapentin (GBP)
Lynch et al. 2014	18	Canada	3 Male and 15 female	56	Allodynia, hyperalgesia, hypesthesia	Chemotherapy-induced neuropathic pain	Unknown	Unknown	Unknown	Analgesics, placitaxel, vincristine, cisplatin

**Table 1**

*Summary of the patient demographics in the selected case studies (continuation)*

Reference	Number of Patients(n)	Country Of origin:	Gender	Mean age (years)	Comorbidities:	Pain Diagnosis:	Previous Cannabinoids Use:	Amount of Cannabis use per month (g)	mean BMI (Kg/m2)	Concurrent Medications:
Bebee et al. 2021	100	Australia	56 male and 44 female	47	None	Acute non-traumatic musculoskeletal pain	No	None	Unknown	Analgesics, oxycodone, paracetamol
Lichtman et al. 2018	397	USA, Germany, Belgium, Hungary, Poland, the UK	214 male and 183 female	59.2	Depression, pancytopenia, pulmonary embolism, pneumonia	Chronic Pain	Unknown	Unknown	26.8	Morphine

Table 1 summarizes some of the patients’ demographics. Most patients that participated in these clinical trials were adults, some of them suffer from major comorbidities such as: depression, pneumonia, anxiety, etc.

**Table 2**

*Summary of the diagnosis, study method and treatment details and outcomes of all patients*

Reference:	Diagnosis:	Method:	Treatment:	Results:
Chaves et al. 2020	Fibromyalgia	Double-blinded, randomized, placebo-controlled	Ingested a few drops of cannabis-rich oil (24.44 mg/ml of THC and 0.51 mg/ml of CBD)	There was a significant improvement on pain relief and a decrease in FIQ score in the cannabis group
Almog et al. 2020	Radiculopathy, diabetic neuropathy, CRPS, phantom/stump pain	Double-blinded, randomized, placebo-controlled, cross-over	Inhaled one of three doses of 0.5 mg, 1.0 mg of THC or placebo	There was a significant pain reduction compared to the placebo group
Abrams et al. 2020	Sickle-Cell Disease	Double-blinded, randomized, placebo-controlled	Inhaled vaporized cannabis 3 times daily for a 5-day period (4.4% of THC and 4.9% CBD)	There was not statistically significance in reduction of pain between the cannabis and placebo groups
Van de Donk et al. 2019	Fibromyalgia	Double-blinded, randomized, placebo-controlled, 4-way crossover	Inhaled vaporized cannabis of 4 distinct varieties	There was no significant pain reduction compared to the placebo group
Selvarajah et al. 2010	Diabetic neuropathy	Double-blinded, randomized, placebo-controlled	Sprayed Sativex (27 mg/ml of THC and 25mg/ml of CBD) four times a day	There was no significant pain reduction compared to the placebo group

**Table 2**

*Summary of the diagnosis, study method and treatment details and outcomes of all patients (continuation)*

Reference:	Diagnosis:	Method:	Treatment:	Results:
Narang et al. 2023	Urinary Calculi	Prospective, double-blinded, randomized, placebo-controlled	Ingested 20 mg of CBD oil (Epidiolex) for 3 days	There was no significant pain reduction compared to the placebo group
Ware et al. 2010	Chronic neuropathic pain caused by surgery or trauma	Double-blinded, randomized, placebo-controlled, Four-period crossover	Inhaled 25 mg of 0%, 2.5%, 6% and 9.4% THC three times daily for 14 days	There was a significant improvement on pain relief in the cannabis group
Turcotte et al. 2015	Multiple Sclerosis	Double-blinded, randomized, placebo-controlled	Ingested (0.5mg/week increase) and 2mg a day of Nabilone for 5 weeks	There was a significant improvement on pain relief in the cannabis group
Lynch et al. 2014	Cancer	Double-blinded, randomized, placebo-controlled, crossover	12 Sprays of Nabiximols (Sativex) per day for four weeks	There was not statistically significance in reduction of pain between the cannabis and placebo groups
Bebee et al. 2021	Acute low back pain	Double-blinded, randomized, placebo-controlled	Ingested 400 mg of CBD	There was no significant pain reduction compared to the placebo group
Lichtman et al. 2018	Cancer	Double-blinded, randomized, placebo-controlled	Sprayed Nabiximols (27mg/ml of THC and 25mg/ml of CBD) for five weeks	There was not a significant difference between the placebo and the cannabis group, but some participants benefited from the cannabis treatment in the secondary endpoint

As it can be seen from table 2., seven studies showed no overall improvement in chronic pain alleviation. Conversely, only four studies showed a significant improvement, whereas only 1 study revealed that 1 cannabis group slightly ameliorate some of the symptoms of chronic pain but there was no overall positive effect of the cannabis treatment compared to placebo. To avoid risk of bias, all the research methods were double-blinded, randomized and placebo-controlled.

### Discussion

Some review articles point out that CBD and THC might have a more positive effect compared to placebo when dealing with acute and chronic pain. In his systematic review

article, Dykukha et al. (2021) argues that nabiximols was more effective than placebo for chronic neuropathic pain alleviation; this review article included 1289 participants. In addition, a meta-analysis was performed to obtain a more accurate statistical interpretation of the results. Therefore, these findings are statistically dependable. Whereas some studies indicate that cannabis-based medicines may be successful when used as an adjuvant therapy. Haleem & Wright (2020) indicate that herbal cannabis and cannabis-based medicines may be efficacious to treat patients who suffer from advanced stages of cancer. Furthermore, it was discovered that when Nabilone was used as an adjuvant therapy, it could notably reduce pain (Tsang & Giudice, 2016). Moreover, a double-blinded, randomized, placebo-controlled trial in patients with fibromyalgia. 17 patients followed a treatment with THC-rich cannabis oil. The results of this study showed that there was significant reduction in pain (Chaves et al., 2020). Likewise, a crossover, randomized, placebo-controlled, double-blinded clinical trial was conducted with diabetic neuropathy and radiculopathy patients to evaluate the efficacy of THC. The study consisted in inhaling small doses of 0.5 mg- 1.0 mg of THC. As a result, pain was significantly reduced compared to placebo (Almog et al., 2020). Similarly, in a crossover, four-period, double-blinded, randomized, placebo-controlled clinical trial, a cannabis treatment demonstrates its efficacy. Twenty-one chronic neuropathic pain patients inhaled 25mg of herbal cannabis for 14 days. The treatment showed favorable results. As a consequence, the analgesic properties of cannabis proved to be advantageous when dealing with chronic pain (Ware et al., 2010). Besides, the efficacy of Nabilone was also analyzed in a randomized, double-blinded, placebo-controlled clinical trial in multiple sclerosis patients. Nabilone was used as an adjunctive to Gabapentin. The Nabilone group showed greater results and was more successful when it was used in combination with Gabapentin in alleviating discomfort than the placebo group. Thus, these results further contribute to the hypothesis that cannabis-based medicines may be useful as an adjunctive therapy (Turcotte et al., 2015).

On the other hand, some other authors argue that cannabinoids might be ineffective for chronic pain treatment. In another systematic literature review, which included 1352 individuals; it was found that eight out of thirteen randomized placebo-controlled trials, cannabis-based medicines appear to have a minimal or no analgesic effect for chronic pain management. However, the authors also pointed out that cannabinoids' analgesic properties could be useful for the treatment of pain of any origin and further exhaustive research was recommended (Longo et al., 2021). Furthermore, some other review articles claim that cannabis is not effective for pain relief. A systematic review on cancer pain evaluated the efficacy of cannabis-based medicines and medical cannabis. It was found that in 1534 cancer patients, THC and Nabiximols did not reduce pain compared to placebo (Haeuser et al., 2019). Nevertheless, some placebo-controlled studies suggest that nabilone might alleviate noncancer pain (Tsang & Giudice, 2016). In addition, in a randomized, double-blinded, placebo-controlled trial in Sickle-cell disease patients



determined that cannabis was statistically no better than placebo in reducing painful symptoms and improving the quality of life. In this clinical trial, participants had to inhale various doses of vaporized cannabis 3 times daily (Abrams et al., 2020). Besides, a 4-way-crossover, randomized, double-blinded, placebo-controlled trials with fibromyalgia patients to assess the effectiveness of vaporized cannabis for the treatment of chronic pain. These findings suggest that medicinal cannabis might not be as powerful as placebo (Van de Donk et al., 2019). Additionally, a randomized, double-blinded, placebo-controlled study for the analysis of Sativex in diabetic neuropathic patients. It was demonstrated that Sativex was no better than placebo in clinical trials (Selvarajah et al., 2010). Similarly, a prospective, randomized, double-blinded, placebo-controlled study was designed to evaluate the benefits of Epidiolex. Participants who underwent a ureteroscopy procedure took part in this study. Patients had to ingest CBD oil (Epidiolex) for three days. The authors concluded that there was no outstanding difference in pain reduction between the cannabis and the placebo treatments. Therefore, administering cannabis to these patients did not reduce pain considerably compared to the placebo treatment (Narang et al., 2023). Correspondingly, in another randomized, placebo-controlled, crossover, pilot trial, Nabiximols (Sativex) was used to treat chemotherapy-induced neuropathic pain in 18 patients. The results of this study revealed that there was no remarkable distinctive outcome between the Nabiximols and the placebo groups. However, only five participants registered a reduction of pain in a responder analysis (Lynch et al., 2014). In addition, a randomized, double-blinded, placebo-controlled trial estimated the analgesic efficacy of CBD as an adjunct medication in patients with acute low-back pain. It was found that the CBD treatment was not better than the placebo treatment (Bebee et al., 2021). Finally, another randomized, double-blinded, placebo-controlled trial of Nabiximols in cancer patients obtained some comparable results from previous studies. The outcome of the Nabiximols treatment was not more successful than the placebo treatment in alleviating chronic pain. Nevertheless, in the secondary endpoint of this study, there were some patients that benefited from the Nabiximols treatment (Lichtman et al., 2018). According to Fisher et al. (2021), there was a 30% of pain reduction in cancer patients. Whereas two placebo-controlled trials showed 50% pain relief in 464 patients. However, the quality of this data was extremely poor. As a result, the authors concluded that there was no overall analgesic effect when the treatment lasted more than seven days (Fisher et al., 2021). Therefore, it appears that medicinal cannabis and cannabis-based medicines are not efficient enough to alleviate discomfort and improve the quality of life of chronic and acute pain patients.

In the contrary, some studies also claim that cannabis-based medicines might have some adverse events. For instance, the use of Nabilone is associated with adverse reactions such as dizziness, euphoria, and drowsiness (Tsang & Giudice, 2016). Moreover, THC has been contraindicated due to some studies involving randomized clinical trials with rodents which concluded that cannabis might cause some mayor harmful effects. In

addition, the use of cannabis-based medicines has been restrained during pregnancy and lactation. Whereas cardiac conditions and psychosis are also listed as contraindications to the use of cannabis (MacCallum & Russo, 2018). Nevertheless, it has been demonstrated that cannabis do not cause overdose and do not represent an elevated risk of addiction (Savage et al., 2016). Nonetheless, there are some evidence that suggests that cannabis may cause addiction. Chronic THC exposure increases the risk of addiction due to changes in neuron morphology. Furthermore, there appears to be some amygdala volumetric and morphological differences between cannabis users and non-cannabis users; these morphological changes might be linked to cannabis use disorder (Zehra et al., 2018). Furthermore, Hill et al. (2022) point out that cannabis abuse might be potentially harmful to psychiatric patients and adolescents. Early exposure to cannabis with high THC content may negatively affect hippocampus development during adolescence and prenatal periods. Contrastingly, there has been a lot of concern about the effects of higher potency and dosage of non-medical cannabis products since the legalization of cannabis in North America. High potency cannabis products can be described as products which have high THC content. As cannabis became legal, the availability of higher potency cannabis products increased over the past few years. Even though causality has not been fully determined, Matheson & Le Foll (2020), argue that cannabis may be associated with psychosis and a portion of cannabis users might develop cannabis use disorder (CUD); however, it is estimated that only 1 out of 10 cannabis users might develop this condition. Cannabis use disorder (CUD) can be defined as a type of condition when a dependence on cannabis is acquired over a prolonged period which can cause intoxication, great distress, and difficulty to complete daily activities (Patel & Marwaha, 2020). Moreover, there seems to be a genetic predisposition for cannabis use disorder (CUD). A large genome-wide association study (GWAS) has shown that CUD is positively correlated with other psychopathologies (Johnson et al., 2020). Some other studies have found a minor difference in the volume of grey matter between cannabis users and cannabis dependent users, but these results have been inconsistent. Another drawback of using cannabis is its effect on heart rate. On the other hand, cannabis appears to be less harmful compared to other drugs such as tobacco and alcohol. For these reasons, it is necessary to keep all cannabis users informed about the possible risks of consuming high potency cannabis products during prolonged periods of time and educate consumers about using the precise dosage to avoid any type of intoxication. Further research is needed to find if there are significant physiological differences between cannabis users and non-cannabis users.

### Conclusion

- These results are consistent with other review articles that claimed that there was not a significant difference between the cannabis and the placebo treatments. More research is needed to obtain a more in-depth understanding of the medicinal

properties of cannabinoids. Furthermore, medicinal cannabis and cannabis-based medicines seem to have a potential as adjunctive therapies. It is crucial to perform more research, so that physicians and the public could be better informed for cannabis-based issues and contraindications.

#### Conflict of interest:

There is no conflict of interest.

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