World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

The clinical use of cannabinoids for pain

Victoria Pereira Simão [1], Gabriel Mota Zamariolli Tavares [2], Gabriel Silva Santos [3,*], Alex Pontes de Macedo [3], Gabriel Ohana Marques Azzini [3], Rafael Barnabé Domingues [3], Rodrigo Cuban de Oliveira [4], Luiza de Sá Narche [5], Lucas Furtado da Fonseca [3,6] and José Fabio Lana [3,7,8,9]

[1] *Department of Anesthesia, Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil.*
[2] *School of Medical Sciences, Lusíada University Center (UNILUS), Santos, SP, Brazil.*
[3] *Department of Orthopedics, Brazilian Institute of Regenerative Medicine (BIRM), Indaiatuba, SP, Brazil.*
[4] *School of Medical Sciences, Ninth of July University (UNINOVE), São Bernardo do Campo, SP, Brazil.*
[5] *School of Medical Sciences, Santa Marcelina University, São Paulo, SP, Brazil.*
[6] *School of Medical Sciences, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil.*
[7] *Regenerative Medicine, Orthoregen International Course, Indaiatuba, SP, Brazil.*
[8] *Clinical Research, Anna Vitória Lana Institute (IAVL), Indaiatuba, SP, Brazil.*
[9] *School of Medical Sciences, Max Planck University Center (UniMAX), Indaiatuba, SP, Brazil.*

World Journal of Advanced Research and Reviews, 2024, 21(03), 1295–1302

Publication history: Received on 28 January 2024; revised on 09 March 2024; accepted on 12 March 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.21.3.0754

Abstract

Cannabis has been used for medicinal purposes more than millennia., further research concerning the potential applications of medicinal cannabis has gained considerable momentum in the medical community. Among the several cannabinoids produced by cannabis leaves, the most notable compounds include Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which act on the endocannabinoid system and play significant physiological roles, such as pain regulation. This manuscript reviews the current knowledge and provides medical evidence about the analgesic potential of medicinal cannabis for chronic pain management. The following databases were searched: MEDLINE, COCHRANE, SCIELO and LILACS. Only randomized controlled trials published within six years were selected. Nine articles met the inclusion criteria for the present review. All nine RCTs reported a significant difference in the reduction in pain intensity; however, only five of the studies reported a significant reduction in pain. The presence of mild-to-moderate adverse events was greater in the intervention groups than in the control group, but these adverse events were well tolerated. The difference in opioid use and other analgesic drugs between the intervention group and the placebo group was not statistically significant. Cannabis-derived compounds promote beneficial effects when administered into patients with chronic pain.

Keywords: Medicinal cannabis; Chronic pain; Cannabinoids; Analgesia; Pain management

1. Introduction

Cannabis sativa (CS) was one of the first plants cultivated by humans and is a feedstock for ancient cultures such as those of the Chou dynasty in northern China. More than 3,000 years ago, it was primarily used in cloth-making as a textile fiber plant or as a food. Since they use it as food, it is quite natural to adapt it for medical purposes [1].

Historically, interest in the medicinal properties of cannabis waned in the early 20th century due to increased government awareness of its illicit use and abuse. This led to the enactment of laws that criminalized its cultivation, processing, and consumption [2].

* Corresponding author: Gabriel Silva Santos

Contemporary research has unveiled the existence of various cannabis species, with *Cannabis sativa* (CS) and *Cannabis indica* (CI) being the most widely consumed in Western society, along with *Cannabis ruderalis* and *Cannabis afghanica*. Each subspecies possesses a distinct chemical composition and varying concentrations of active compounds [3]. Terpenophenolic cannabinoid compounds, for instance, are exclusive to *Cannabis sativa*. Among the more than 70 cannabinoids produced by plants, the most abundant are *Δ9-tetrahydrocannabinol* (THC), known for its potent psychoactive properties, and *cannabidiol* (CBD), which has anxiolytic and analgesic qualities [4].

The clinical effects associated with cannabis administration are primarily attributed to its chemical interaction with the *endocannabinoid system* (ECS). The ECS consists of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and enzymes responsible for cannabinoid synthesis and metabolism. This system is pivotal for global physiological regulation, impacting neurological and immunomodulatory signaling and influencing processes related to appetite, motor function, pain transmission, and fertility [4]. Most of the effects of cannabinoids and endocannabinoids involve two G protein-coupled cannabinoid receptors: CB1 and CB2. These receptors are widely distributed throughout the body but differ in their location. CB1 is abundant in the central and peripheral nervous systems, while CB2 is more prevalent in various organs and tissues, particularly those involved in immune-related functions [5].

ECS components have been identified extensively through nociceptive pathways that act directly on endogenous pain control, making them attractive alternatives comparable to traditional analgesic therapies [6].

Thus, cannabinoids may be applied for chronic pain relief and for neuroinflammation in some neurological diseases, such as multiple sclerosis, Huntington's disease, muscle spasms and stiffness, and for dysregulation of the dopamine-receptor signaling cannabinoid [7].

Due to the emergence of recent studies and interventions, different cannabis-derived pharmaceuticals, such as *dronabinol*, *nabilone*, and *nabiximols*, have been found to exist via several routes of administration (ROA), namely, intradermal, oral and respiratory [8].

Despite the availability of cannabis-derived pharmaceuticals, opioids are widely administered for chronic pain management, but as such, they are not without serious concern. The opioid epidemic is, without a doubt, a major public health challenge currently faced by healthcare professionals, policymakers and, most importantly, patients [9]. Patients afflicted by chronic pain who undergo opioid therapies are subject not only to tolerance, physical dependence, and hyperalgesia but also to the risk of drug abuse, adverse immunomodulatory effects, hormonal changes, sleep disturbances and psychomotor disorders [10]. Finally, the use of cannabinoids may be an alternative to the epidemic of opioids, which are widely prescribed for chronic pain [9].

Objectives

- Primary objective

To evaluate the efficacy of chronic use of cannabis solutions for chronic pain.

- Secondary objective

To evaluate the safety of the use of cannabis solutions for chronic pain.

2. Materials and methods

2.1. Literature search

In this review, strategies were established to search the literature, as described in Table 1. The following databases were used: MEDLINE, COCHRANE, SCIELO and LILACS. The search had a cutoff date of July 31st, 2022.

2.2. Eligibility criteria

Nine randomized controlled trials (RCTs), double-blind and placebo-controlled, with human subjects published from July 1st, 2016, through July 31st, 2022 were included. Only articles in English, Spanish or Portuguese were considered. Studies without access to the full text were excluded from the analysis. A review of nine publications was carried out to assess whether the use of cannabis-derived drugs is associated with the improvement of chronic pain.

2.3. Characteristics of the selected studies

The data of a total of 823 patients (N) with various conditions, all of whom had chronic pain, were analyzed as follows: advanced cancer (n=397), central nervous system injury (n=240), spinal cord injury (n=42), diabetic neuropathy (n=37), sickle cell anemia (n=23), complex regional pain (n=6), neuropathy of the extremities (n=29), HIV-associated neuropathic pain (n=32) and fibromyalgia (n=17). Of the total 823 patients, 447 patients received placebo, and 458 patients received an active drug (199 received nabixomol oral spay, 124 received dronaminol, 96 received vaporized cannabis, 16 received cannabidivarin, 15 received topical CBD oil, and 8 received oral cannabis oil). Some trials submitted the entire sample both for intervention and comparison (Cannabis and Placebo, respectively) during the course of the analysis period, as shown in Almon et al. (2020), Wallace et al. (2020) and Wilsey et al. (2016). The follow-up period ranged from 120 hours to 16 weeks (Table 2).

3. Discussion

3.1. Pharmacokinetics

THC is a highly lipophilic substance that can accumulate in many tissues, such as the heart, liver, spleen and adipose tissue; the last two types of tissue serve as long-term storage sites. Additionally, high concentrations can be found in cerebral tissue as they cross the blood–brain barrier [11].

The main forms of Δ9-THC were administered via oral and respiratory routes. When inhaled, the compound rapidly enters the circulation, and its blood plasma levels increase within 1-2 minutes after the first inhalation. However, when Δ9-THC is ingested, it peaks in the circulation within 1-2 h, with lower plasma levels in comparison to those of the inhalation method [11].

Experimental findings demonstrated that inhaling puffs from a 3.5% Δ9-THC cigarette led to notable increases in plasma levels, reaching approximately 270 ng/mL. This effect was particularly pronounced when the THC concentration was maintained at doses of 1.75% or 3.55%. However, the blood plasma levels at higher doses exhibited variability, ranging from levels lower than 90 ng/mL to levels exceeding 250 ng/mL. This variation suggests that the bioavailability and suitability of Δ9-THC and other cannabinoids for an individual's health depend on intrinsic factors such as sex, age, body mass, metabolic health, and physiological background [11].

3.2. Analgesia

CB1 and CB2Rs are known as cannabinoid receptors, but the data regarding CB1 receptors are inconsistent, and it is important to note that CBD is not an agonist of these receptors. CB1 receptors are located primarily in the central nervous system (CNS) and are less prevalent in peripheral areas, although they are associated with sensory neurons.

In several studies, capsaicin (CAP) has been used to investigate peripheral pain responses. It is now understood that cannabinoids directly interact with transient receptor potential (TRP) channels, including transient receptor potentials of vanilloid types 1 and 2 (TRPV1 and TRPV2) and transient receptor potential of ankyrin type 1 (TRPA1). These TRP channels are primarily found on sensory neurons and, interestingly, alongside cannabinoid receptors. This interaction leads to depolarization, followed by sensitization and subsequent inhibition. Importantly, this mechanism does not rely on G proteins but may instead depend on Ca2+/calcineurin, suggesting a direct mode of action reminiscent of capsaicin (CAP) [11].

In a study by Wilsey et al., patients with spinal cord injuries were analyzed, and they were subjected to three inhalation sessions of vaporized cannabis containing a placebo, 2.9% THC, or 6.7% THC. One hour after the first session, pain intensity was significantly lower for both active treatment doses than for the placebo ($p < 0.05$). Notably, the effects of the highest THC dose remained significant for the following two hours ($p < 0.01$). The number needed to treat (NNT) to achieve a 30% pain reduction over an 8-hour period was 4 (95% CI: 2.1-25.3) for the lowest dose versus placebo and 3 (95% CI: 1.6-4.2) for the highest dose versus placebo. However, there was no significant difference in the impact on pain between the lowest and highest THC doses ($p > 0.11$) [12].

Additionally, it was found that relief from spasticity was more pronounced with the 2.9% THC dose than with the 6.7% THC dose. Neuropathic Pain Scale (NPS) measurements demonstrated that vaporized cannabis had a positive and significant effect on all the multidimensional pain descriptors assessed. In regard to the modeling of pain intensity, cold sensations, and superficial pain, there was a substantial reduction in pain levels after both active treatments compared to the placebo (p values ranging from <0.0001 to 0.048). The sequence in which treatments were administered had a significant impact on pain intensity and superficial pain, but even after controlling for the treatment sequence, the

effects of the THC dose persisted. Immediately after the first vaporization, NPS effects included sensations of burning, cold, itching, deep pain, and superficial pain ($p < 0.05$), with variations depending on the THC dose. Several of the psychoactive and subjective adverse effects, such as nausea, altered time perception, increased appetite, memory impairment, euphoria, confusion, and reduced focus, were found to be dose dependent, with more pronounced effects observed at higher THC doses. Given the evidence that the 2.9% and 6.7% THC doses did not significantly differ in terms of analgesic potency, it is reasonable to conclude that patients with spinal cord injuries seeking to prevent psychomimetic effects should receive a lower THC dose.

Schimrigk et al. conducted an analysis involving individuals suffering from neuropathic pain in a controlled and double-blind phase in which patients in the intervention group received dronabinol treatment for 16 weeks. The second phase of the study involved both the comparison group and the intervention group in an open-label trial; the patients were exposed to dronabinol for 32 weeks, after which the treatment was extended to 96 weeks. In this randomized controlled trial (RCT), there was a clinically significant reduction in mean pain intensity over the 16 weeks of dronabinol and placebo treatment, although no statistically significant difference was observed between the two groups [13].

The assessment of quality of life using the SF-36 indicated a noticeable improvement during the double-blind period, from the study's outset until the conclusion of the treatment, in both the dronabinol and placebo groups, and these improvements did not significantly differ between the groups. During the double-blind phase, there was a greater percentage of patients who experienced adverse effects in the dronabinol group than in the placebo group. This initial increase in side effects was attributed to the titration period and the high expectations of the patients [13].

Despite the prolonged intake of dronabinol, only ten patients experienced transient withdrawal symptoms. Furthermore, there was no documentation of misuse, and only one patient exhibited mild manifestations of dependence. The consistent ingestion of dronabinol over an extended period suggested that tolerance to the drug did not develop [13].

Lichtman et al. conducted a study examining the use of an oral spray containing a different cannabinoid, *nabiximols*, in comparison to a placebo in patients with advanced cancer and severe, unmanageable chronic pain. The study spanned a 2-week period during which patients self-titrated their medications, followed by a 3-week treatment phase at a stable dose. While *nabiximols* did not significantly enhance the mean NRS (numeric rating scale) score for pain ($p = 0.253$) or the worst NRS score for pain ($p = 0.678$), they did demonstrate a notable improvement in the NRS score for sleep disturbances ($p = 0.027$) [14].

In comparison to preclinical studies that suggested that a combination of opioids and cannabinoids could produce analgesic effects, the *nabiximols* in this study did not exhibit opioid-sparing effects. The safety of nabiximols was consistent with the findings of previous studies in patients with advanced cancer, and no new safety concerns arose. The most commonly reported adverse effects included gastrointestinal symptoms (nausea and vomiting) and nervous system disorders (dizziness). Notably, there was no evidence of abuse or misuse of *nabiximols* and no reports of treatment-emergent suicidal behaviors or actual suicides in the active treatment group [14].

Xu et al. conducted a study to assess the effectiveness of applying topical CBD oil (250 mg/3fl.oz) in patients with peripheral neuropathy over a 4-week period. The CBD treatment group showed a significantly greater mean reduction in three domains than did the placebo group: intense sensations ($p = 0.009$), sharp sensations ($p < 0.001$), and itching ($p = 0.001$). In addition, a statistically significant decrease in scores from baseline to over time was noted in the CBD group in the following NPS domains: sharp sensation ($p = 0.025$), unpleasant sensation ($p = 0.018$), and superficial pain ($p = 0.013$). There was a notable mean reduction in deep pain from baseline in the CBD treatment group compared to the placebo group ($p = 0.064$), even though this difference was not statistically significant. Importantly, no side effects were described during this trial [15].

Abrams et al. investigated the outcomes of vaporized cannabis in patients with sickle-cell anemia who suffered from chronic pain. The study involved two inpatient stays of 5 days and 4 nights at a clinical research center, with at least a 30-day interval between stays. During the first session, participants inhaled vaporized cannabis three times a day at specific times, and during the following stay, they inhaled placebo vaporized cannabis for similar durations. The difference in the mean pain rating, as measured by the visual analog scale (VAS), between the active and placebo groups was not statistically significant. There were no statistically significant differences in pain interference scores between cannabis and placebo during days 1 to 5 for common routine activities, but there was a significant decrease in interference with mood. Participants in the study generally used at least one opioid analgesic at baseline, which they continued to receive as needed during their admissions, and the mean difference between cannabis and placebo periods was not significant [16].

Most adverse effects reported in the study were mild and self-limiting, scoring below 1 on a scale of 1 to 3. The most common side effect was sedation, and there were no significant differences in the average aggregate adverse effect scores between the cannabis and placebo periods. The treatment was generally well tolerated [16].

Almog et al. described a study in which a single dose of 0.5 mg or 1.0 mg of vaporized THC was provided and compared to a placebo. The trial evaluated analgesic potency, specifically the change in pain intensity from baseline, in patients with chronic focal neuropathic pain, distal symmetric (diabetic) neuropathic pain, or complex regional pain syndrome. Blood samples were collected to measure THC plasma levels at various time points, from baseline to 150 minutes after inhalation. The study reported a dose-dependent pharmacokinetic profile and revealed a decrease in pain intensity in patients with chronic neuropathic pain and complex regional pain syndrome in response to inhalation of small doses of a cannabis-derived compound. Clinically significant reductions in pain of 25% and 39% were observed after inhalation of 0.5 mg and 1.0 mg THC, respectively. Importantly, there was no consistent documentation of cognitive impairment based on the Cambridge Cognition Battery Test. Most adverse effects were classified as mild, with the most common reported experiences being 'euphoria', 'coughing', 'weakness', 'restlessness', 'dry mouth', and 'dizziness.' This trial provides evidence that patients with chronic pain can benefit from low doses of THC [17].

Wallace et al. conducted a study involving patients with painful diabetic neuropathy who participated in four treatment sessions spaced two weeks apart. During these sessions, the participants were assigned to one of four interventions: placebo or cannabis at different THC concentrations (1% THC as "low," 4% THC as "medium," and 7% THC as "high"). A randomized controlled trial (RCT) revealed that the average pain intensity score in the placebo group was 0.44 points greater than that in the low-dose group ($p = 0.031$), 0.42 points greater than that in the medium-dose group ($p = 0.04$), and 1.2 points greater than that in the high-dose group ($p < 0.001$). Moreover, there was no statistically significant difference between the low-dose and medium-dose groups ($p = 0.92$). However, the average pain score in the high-dose group was significantly lower by 0.73 and 0.75 points than that in the low-dose and medium-dose groups, respectively (both $p < 0.001$) [18].

Chaves et al. conducted a double-blind randomized trial over an 8-week period to assess the effects of THC-rich cannabis oil (containing 24.44 mg/mL THC and 0.51 mg/mL CBD) on the symptoms and quality of life of women with fibromyalgia. The initial daily dose was one (approximately 1.22 mg of THC and 0.02 mg of CBD), and subsequent adjustments were made based on the symptoms. The Fibromyalgia Impact Questionnaire (FIQ) was used as the assessment tool. The cannabis group exhibited a significant decrease in FIQ score ($p < 0.001$), and compared to the placebo group, this decrease was also significant ($p = 0.005$). The questionnaire indicated significant improvements in well-being, pain relief, motivation, and fatigue scores in the cannabis group. In contrast, the placebo group showed improvements in depressive symptom scores, and there were no intolerable side effects [5].

Eibach et al. also conducted an 8-week double-blind randomized trial with two phases (4 weeks each) involving the treatment of HIV-associated neuropathic pain with 400 mg/day cannabidivarin (CBDV). The first phase used an 11-point numeric rating scale, and the secondary endpoints included additional pain medication, pain characteristics, and quality of life. In the CBDV group, pain intensity was 0.62 points greater than that in the placebo group ($p = 0.16$, 95% confidence interval -0.27 to 1.51). In the second phase, CBDV did not appear to affect the amount of additional pain medication, pain characteristics, or quality of life. The side effects were similar in both groups. The authors attributed the lack of efficacy of CBDV treatment in treating HIV-associated neuropathic pain to the absence of CB receptor activation, and the differences observed were not statistically significant [19].

All nine RCTs reported a significant difference in pain intensity, but the difference in pain intensity reduction between patients who received cannabinoids and patients who received placebo was significant in only five of the studies. The measurements were analyzed using the NRS-11, VAS and SF-36 assessment tools. These findings corroborate the findings of Mücke et al. and Aviram, who reported statistically significant improvements in mood, pain severity, burning sensations and itching. The presence of mild-to-moderate adverse events was greater in the intervention groups than in the control group, but these adverse events were well tolerated. Of the 434 patients who underwent the intervention, only 10 had transient withdrawal effects, and 1 had mild symptoms of dependence, supporting the findings previously described in other reviews and meta-analyses that the use of cannabinoid derivatives is safe [20,21]. Furthermore, RCTs in which titrated doses of THC were used revealed that the reduction in pain intensity is dose dependent and that lower doses convey more benefits and fewer adverse effects [17,18]. No statistically significant difference was detected in the reduction in the use of opioids or other analgesic drugs in the intervention group. However, as people with chronic pain tend to use several drugs with greater systemic adverse effects, future larger and longer investigations are highly warranted. The potential use of cannabis-based interventions for chronic pain patients must be further elucidated to help alleviate the ongoing public health crisis related to opioid overuse. One of the limitations of this review is the heterogeneity of the sample across the studies, which included patients with chronic pain associated with various

conditions, such as advanced cancer, neuropathic central nervous system injury, spinal cord injury, diabetic neuropathy, sickle cell anemia, complex regional pain syndrome, fibromyalgia and HIV-associated neuropathic pain. The use of different concentrations of CBD and THC, treatment schemes, and follow-up periods were also limiting factors. Last, most of the studies had small sample sizes; a larger sample size is needed to make the data more robust [16].

Abbreviations

- Δ9-THC,
- Δ9-tetrahydrocannabinol;
- AAE, Absence of adverse events;
- AAE, Adverse events;
- ARAE, Absence of reduction of adverse effects;
- CAP, Capsaicin;
- CBD, Cannabidiol;
- CBVD, Cannabidivarin;
- Ci, Cannabis indica;
- CI, Confidence interval;
- CO, Cannabis oil;
- CS, *Cannabis sativa*;
- DE, Decreased spasticity;
- DPI, Daily pain improvement;
- DRP, Dose-dependent reduction in pain intensity;
- ECS, Endocannabinoid system;
- FIQ, Fibromyalgia Impact Questionnaire;
- IS, Improved symptoms;
- IM, Improved mood;
- LDT, Low dose of THC;
- N, number of patients;
- NNT, Number needed to treat;
- NPS, Neuropathic Pain Scale;
- NRP, No reduction in pain intensity;
- NRS-11, Numeric Rating Scale;
- QL, Improved quality of life;
- RCT, Randomized Controlled Trials;
- ROA, Routes of administration;
- RS, Reduction of intense, sharp, cold, and itchy sensations;
- RSEP, Reduction of spontaneous and evoked pain;
- SF-36, The quality-of-life assessment;
- SI, Sleep improvement;

4. Conclusion

This review suggested that cannabis-derived compounds promote beneficial effects when administered to patients with chronic pain. The presence of mild adverse effects was not considered a limiting factor, and even when they did occur, they were considered safe and well tolerated. In many countries, cannabinoid derivatives are still limited and expensive. Therefore, future investigations with larger and more representative samples and longer follow-up periods should be conducted. With the improvement of evidence about the use of cannabinoids for pain treatment, investigative trials should be conducted, allowing a better analysis of the safe and effective dose and ROA. This will help explore the therapeutic potential of cannabis-based interventions for chronic pain, envisioning greater patient well-being and a possible solution for the current opioid crisis.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

References

[1] Li H-L. An archaeological and historical account of cannabis in China. Econ Bot [Internet]. 1973 [cited 29 September 2022]; 28: 437–48. Available at: http://link.springer.com/10.1007/BF02862859

[2] McDonagh MS, Morasco BJ, Wagner J, et al. Cannabis-Based Products for Chronic Pain : A Systematic Review. Ann Intern Med. 2022; 175: 1143–53.

[3] Kim PS, Fishman MA. Cannabis for Pain and Headaches: Primer. Curr Pain Headache Rep. 2017; 21: 19.

[4] Brown MRD, Farquhar-Smith WP. Cannabinoids and cancer pain: A new hope or a false dawn? Eur J Intern Med. 2018; 49: 30–6.

[5] Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Pain Med. 2020; 21: 2212–8.

[6] De Aquino JP, Ross DA. Cannabinoids and Pain: Weeding Out Undesired Effects With a Novel Approach to Analgesia. Biol Psychiatry. 2018; 84: e67–9.

[7] Lötsch J, Weyer-Menkhoff I, Tegeder I. Current evidence of cannabinoid-based analgesia obtained in preclinical and human experimental settings. Eur J Pain. 2018; 22: 471–84.

[8] Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy. 2013; 33: 195–209.

[9] Johal H, Devji T, Chang Y, Simone J, Vannabouathong C, Bhandari M. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020; 13: 1179544120906461.

[10] Kraychete DC, Garcia JBS, Siqueira JTT de. Recommendations for the use of opioids in Brazil: Part IV. Adverse opioid effects. Rev dor [Internet]. 2014 [cited 21 December 2022]; 15: 215–23. Available at: http://www.scielo.br/j/rdor/a/pSMBBGPmL4ThRHrG6ghh9ps/?format=html

[11] Amin MR, Ali DW. Pharmacology of Medical Cannabis. In: Bukiya AN, Ed. Recent Advances in Cannabinoid Physiology and Pathology [Internet]. Cham: Springer International Publishing; 2019 [cited 16 November 2022]: 151–65. (Advances in Experimental Medicine and Biology). Available at: https://doi.org/10.1007/978-3-030-21737-2_8

[12] Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease. The Journal of Pain [Internet]. 2016 [cited 16 November 2022]; 17: 982–1000. Available at: https://www.jpain.org/article/S1526-5900(16)30072-4/fulltext

[13] Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. ENE [Internet]. 2017 [cited 16 November 2022]; 78: 320–9. Available at: https://www.karger.com/Article/FullText/481089

[14] Lichtman AH, lux EA, McQuade R, et al. The results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. Journal of Pain and Symptom Management [Internet]. 2018 [cited 16 November 2022]; 55: 179-188.e1. Available at: https://www.jpsmjournal.com/article/S0885-3924(17)30465-7/fulltext

[15] Xu DH, Cullen BD, Tang M, Fang Y. The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. Curr Pharm Biotechnol. 2020; 21: 390–402.

[16] Abrams DI, Couey P, Dixit N, et al. Effect of Inhaled Cannabis for Pain in Adults With Sickle Cell Disease: A Randomized Clinical Trial. JAMA Network Open [Internet]. 2020 [cited 16 November 2022]; 3: e2010874. Available at: https://doi.org/10.1001/jamanetworkopen.2020.10874

[17] Almog S, Aharon-Peretz J, Vulfsons S, et al. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial. European Journal of Pain [Internet]. 2020 [cited 16 November 2022]; 24: 1505–16. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ejp.1605

[18] Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. J Pain [Internet]. 2015 [cited 16 November 2022]; 16: 616–27. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5152762/

[19] Eibach L, Scheffel S, Cardebring M, et al. Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial. Clinical Pharmacology & Therapeutics [Internet]. 2021 [cited 16 November 2022]; 109: 1055–62. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/cpt.2016

[20] Aviram J, Samuelly Leichtag G. Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain Physician. 2017; 20: E755–96.

[21] Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews [Internet]. 2018 [cited 5 November 2023]; Available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012182.pub2/full

Appendix

Table 1 Literature search strategy

MEDLINE: (cannabidiol) OR (cannabinoids) OR (cannabis sativa) OR (delta-9-tetrahydrocannabidiol) OR (CBD) OR (THC) AND (pain)
SCIELO: (cannabis) AND (pain)
COCHRANE: (cannabis) AND (pain)
LILACS: (cannabidiol) OR (cannabis) AND (pain)

Table 2 Study characteristics

Reference	Study desing	Intervention	Control	Follow-up	Outcome
Wilsey, 2016	ECR	VC (THC)	Placebo	120 Hours	SPR; AE; RS; DE
Schimrigk, 2017	ECR	Dronabinol	Placebo	16 Weeks	STO; AE;
Lichtman, 2017	ECR	Nabiximol	Placebo	5 Weeks	DPI; SI; STO; AE
Xu, 2019	ECR	TO (CBD)	Placebo	4 Weeks	RS; STO; AAE;
Abrams, 2020	ECR	VC (THC+CBD)	Placebo	5 Days	STO; IM
Almog, 2020	ECR	VC (THC)	Placebo	8 Weeks	DRP; STO; LDT; AE
Wallace, 2020	ECR	VC (THC)	Placebo	8 Weeks	DRP; RSEP; AE
Eibach, 2020	ECR	CBDV	Placebo	13 Weeks	NRP; ARAE
Chaves, 2020	ECR	CO (THC+CBD)	Placebo	8 Weeks	SPR; IS; IQL

AAE: Absence of adverse events/AE: Adverse events/ ARAE: Absence of reduction of adverse effects/CBVD: Cannabidivarin/CO: Cannabis oil/DE: Decreased spasticity/DPI: Daily pain improvement/DRP: Dose-dependent reduction in pain intensity/IQL: Improved quality of life/IM: Improved mood/IS: Improved symptoms/LDT: Low dose of THC/NRP: No reduction in pain intensity/RS: Reduction of intense, sharp, cold, and itchy sensations/RSEP: Reduction of spontaneous and evoked pain/SI: Sleep improvement/SPR: Significant pain reduction/STO: Safe treatment option/TO: Topical oil/VC: Vaporized Cannabis