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Review

J Clin Med Res. 2020;12(6):344-351

A Scoping Review on Clinical Trials of Pain Reduction With Cannabis Administration in Adults

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Abstract

Indications of cannabis use are numerous although the indication to relief pain remains a major research interest and clinical application. Studies investigating the effect of herbal cannabis and cannabis-based medicine on neuropathic, non-neuropathic pain, acute pain and experimentally induced pain were reviewed. A search was performed in PubMed and Cochrane library for articles published in English between January 1, 2000 and May 8, 2020. The search terms used were related to cannabis and pain in adults. We identified 34 studies, of which 30 were randomized controlled clinical trials (RCTs). Varying effects were identified from the RCTs, and as expected more promising effects from non-RCTs. Cannabis-based medications were found most effective as an adjuvant therapy in refractory multiple sclerosis, and weak evidence was found to support the treatment of cancer pain especially in advanced stages. Chronic rheumatic pain showed promising results. Adverse events of cannabis-based treatment were found to be more frequent with tetrahydrocannabinol herbal strains compared to other cannabis-derived products.

Keywords: Cannabidiol; Dose; Safety; Pain; Cannabis

Introduction

Medical cannabis or medical marijuana refers to the use of the cannabis plant, parts, extracts, or materials from the plant (buds, resin, etc.). Cannabis extracts contain a number of phytocannabinoids comprising tetrahydrocannabinol (THC) and cannabidiol (CBD), while extracts with standardized content of THC or THC/CBD are better classified as "cannabis-derived or -based" [1]. Nabiximols (Sativex®), a registered medical cannabis extract, is an example of cannabis-based medicine. It is obtained from whole plant extracts and delivers an approximate equal amount of THC and CBD. It also contains trace quantities of some minor cannabinoids (CBs), such as cannabichromene, cannabino and cannabigerol [2]. CBs can be synthetic, semisynthetic or plant-derived, however, are defined as single pharmaceutical compounds [3]. Dronabinol is a plant-derived semi-synthetic CB (THC) and Namisol® is an oral tablet containing pure THC (> 98%). Other compounds such as modulators of the endocannabinoid system are under development.

Cells in damaged tissues produce endocannabinoids which are able to modulate pain signals by moderating both sensitization and inflammation via the initiation of CB receptors also targeted by THC and CBD [4]. CB_1 receptors modulate neurotransmitter release in the brain and spinal cord and are present in sensory neurons of the dorsal root ganglion and trigeminal ganglion and in vital immunological cells, e.g. macrophages. CB_2 receptors are expressed at considerable levels in cells of hematopoietic origin and very few CB_2 receptors are present in the tissues of the central nervous system, but have seen to increase in response to peripheral nerve damage [5]. Endocannabinoids, anandamide and 2-arachidonoyl-*sn*-glycerol (2-AG) are produced in damaged tissue by activation of CB receptors. Anandamide can act as an autocrine or paracrine messenger and can be broken down to arachidonic acid and ethanolamine or, directly transformed by COX-2 into proalgesic prostamides; from here it modulates nociceptive signals by activating local CB_1 receptors. The 2-AG is formed by the hydrolysis of phosphatidylinositol-4,5-biphosphate and plays a prominent role in the descending modulation of acute pain. Anandamide and 2-AG are recruited during tissue injury to provide a first response to nociceptive signals. Hence, the endogenous CB system is a key stone in understanding the efficacy of exogenous CBs, e.g. those found in the cannabis plant. In summary, the assumed rationale for CBD is whole-body exposure to exogenous CBs to inhibit pain.

The legalization of cannabis for either medical or recreational use in US and Canada has propelled also the public interest in the use of cannabis products. Herbal cannabis, plant derived and synthetic products are proposed for use in a variety of conditions, but the most researched areas are in the field of pain management and multiple sclerosis [6, 7]. Pain relief is the most cited reason for cannabis use and a wide-spread exists in patient-communities and organizations that cannabis has been helpful to their chronic, acute or cancer-related pain condition [8]. Despite this, very few countries have approved cannabis products for pain management. In the EU, few countries indicate pain and an indication for herbal cannabis pre-

Manuscript submitted May 11, 2020, accepted May 25, 2020
Published online June 4, 2020

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doi: https://doi.org/10.14740/jocmr4210

scription. Dronabinol is approved for use in cancer pain in Denmark and can be prescribed for any type of chronic pain in Germany [1].

To understand the effects and harms related to the use of cannabis for pain, we conducted an extensive search of the published literature and registered clinical trials (Supplementary Materials 1 and 2, www.jocmr.org).

Methods

One author (RW) searched PubMed, Science Direct and Springer for published trials including registered clinical trials on www.clinicaltrials.gov. Keywords and MESH terms referenced to cannabis and clinical management of pain were employed. In addition, information from registered trials up to December 2019 were retrieved and included in this scoping review.

We extracted the following data: condition and symptoms, year of publication, country, study population, number of patients, age, gender, weight, outcome measures, effect of treatment, side effects, dosage, administration form (pills, smoking, oil, etc.), length of treatment, doses and product/brand.

Results

Herbal cannabis - THC

The effect of smoked herbal cannabis was assessed in two studies, both of which are randomized, placebo-controlled and double-blinded. Abrams et al assessed the effect of smoking cannabis cigarettes on chronic pain in 55 human immunodeficiency virus (HIV)+ patients presenting painful sensory neuropathy. Cannabis cigarettes (3.56% THC) were smoked three times a day for 5 days. Significant differences were observed in pain intensity and on the percentage of patients achieving 30% reduction in pain intensity, when compared to placebo [9]. In both studies patients continued their treatment regime for painful symptoms. Cannabis treatment with different concentrations of THC in the second study was proceeded by a period of titrating the most well tolerated dose. The authors found a reduction in pain intensity measured by descriptor differential scale compared to placebo. Smoking cannabis was well tolerated, and most side effects were mild in nature [10].

In another randomized, placebo-controlled, cross-over trial, 37 patients with multiple sclerosis were assessed for pain reduction after smoking herbal cannabis with 4% THC by weight daily. Treatment consisted of smoking a marijuana cigarette once a day for 3 days. Smoked cannabis significatively reduces pain scores on a visual analogue scale (VAS) compared with placebo [11].

Similarly, short-term effects of inhaled cannabis with different concentrations of THC (1%, 4% and 7%) were assessed in 16 patients with painful diabetic peripheral neuropathy. This was a randomized, placebo-controlled, cross-over trial. Spontaneous and evoked pain scores were measured using a VAS. A significant difference was observed between all doses and placebo for spontaneous pain, and between high dose and placebo for evoked pain. Adverse events were reported only for high THC doses, which were euphoria and somnolence [12].

In another randomized, placebo-controlled, cross-over trial that involved 55 patients with central and peripheral neuropathic pain, the effect of smoked cannabis was assessed on a VAS. An analgesic response to smoking cannabis was observed for both low and high content of THC compared to placebo. The response began to reverse within 1 - 2 h after the last dose. At the higher dose (7% THC), cognitive effects were observed, particularly memory alteration; however, the psychoactive effects were minimal [13]. Forty-two subjects with central neuropathic pain related to spinal cord injury and disease were assessed for pain reduction after a 3-h session where patients were delivered vaporized herbal cannabis containing 2.9% or 6.7% THC. A significant effect was observed on pain intensity measured with an 11-score numerical rating scale (NRS-PI). Different THC concentrations did not show a difference in analgesic potency; however, the higher doses were associated with psychoactive and subjective effects [14].

Cannabis-based medicine

Neuropathic pain - THC-CBD combinations

Nabiximol (2.7 mg THC and 2.5 mg CBD/100 µL) was administered sublingually in four studies for the treatment of multiple sclerosis (MS)-related neuropathic pain. One study, a randomized, placebo-controlled, cross-over trial, assessed the effect of chronic administration of nabiximol on induced neuropathic pain in 18 patients with MS. The patients were instructed to self-titrate the active drug without exceeding 48 sprays during a 24-h period. Comparison with placebo showed small but statistically non-significant effects of treatment on 10-point VAS scores, and no adverse events. Drowsiness, slower thinking, or both, as well as dizziness and vertigo were more frequently reported in the cannabis group than the placebo group [15].

In a similar study, 160 patients with MS were randomly assigned to placebo or active treatment that consisted of 2.7 mg THC and 2.5 mg CBD administrated sublingually using a spray. Patients were required to self-titrate gradually up to a maximum of 120 mg THC and 120 mg CBD per day. Patients on active treatment at the end of a 6-week period showed a significant reduction of pain assessed by VAS score compared to placebo. Intoxication levels were mild and no significant difference in the cognition and mood adverse events could be detected between groups [16].

Twenty-four patients with a diagnosis of progressive MS were assessed in a 4-week treatment course with cannabis-based medical extract in a randomized, placebo-controlled, dose-titrate, parallel-group trial. The drug was administered in oral capsules containing 1.5 and 5 mg THC three times a day. A minority of patients reached the maximum dose allowed per day (24 mg THC) while others received only 15 mg THC/day. Pain was reduced when measured with an NRS directly after

the administration of cannabis-based medicine in the clinic. No serious adverse event during the treatment period was observed [17].

The effect of oral cannabis-based medicines on neuropathic MS patients was assessed in two randomized, placebo-controlled, parallel-group studies. Both studies were preceded by a dose titration phase. Cannabis-based medical extracts oral capsules containing 2.5 mg THC and 0.8 - 1.8 mg CBD (commercial name Connador) were administered daily for a maximum dose of 25 mg/day. The first study had a duration of 12 weeks maintenance phase. The neuropathic pain assessed with category rating scale was significatively improved compared to placebo [18]. Similar doses were used in the second study with an additional arm receiving synthetic THC. Data on reported pain on an 11-point rating scale showed a significant improvement for the two treatment groups compared to placebo and no significant treatment-related side effects were reported [19].

The effect of nabiximol was assessed in 30 patients with diabetic peripheral neuropathy. The doses were not reported; however, the total duration of the study was 12 weeks with 2 weeks dose titration followed by 10 weeks of maintenance. The CBD was an adjuvant to pre-existing neuropathic pain treatment. When compared to placebo, no statistically significant improvement in pain scores was observed [20].

Nabiximol's effect on neuropathic pain in a 15-week randomized, double-blind, placebo-controlled, parallel-group study showed an effect of active treatment measured as the 30% responder level in favor of active treatment compared to placebo. The other outcome-measure, the reduction in mean of NRS scores did not reach statistical significance [21]. A similar study assessed the effect of nabiximols in 125 patients with peripheral neuropathic pain. The mean reduction in pain intensity score was greater in patients receiving nabiximols compared to placebo [22].

A randomized, placebo-controlled, parallel-group trial assessed the effect of nabiximol in MS patients using similar modalities as the previous mentioned studies on pain modulation. Significant pain reduction after a treatment period of 4 weeks was found favoring the CBD group. Two patients withdrew from the intervention arm, one of whom dropped due to adverse events [23]. A third trial assessed the effect on pain in a 14-week duration, randomized, placebo-controlled, parallel-group study. The effect of nabiximol as an adjuvant treatment on MS-related neuropathic pain was assessed. At the end of treatment, a small difference in the number of responders at the 30% improvement level in mean pain NRS score was reported, yet not statistically significant. The difference in the incidence rate between treatment with CBD and placebo was statistically insignificant [24].

Cancer pain

A two-phase study (two studies incorporated in one design) assessed the effect on cancer pain not responsive to conventional opioid-based treatment. The active treatment consisted of oromucosal spray of cannabis extract (Sativex) over a 3-week period. The first phase (study 1) was a conventional randomized, placebo-controlled, parallel-group study, while the second phase (study 2) was enriched enrolment with a randomized withdrawal design. In study 1, patients were randomized to Sativex or placebo, and in study 2, all patients self-titrated Sativex over a 2-week period. From here, patients with a $\geq$ 15% improvement from baseline in pain score were then randomized 1:1 to Sativex or placebo, followed by a 5-week treatment period. Mean change on average pain scores and percent improvement did not show a significant difference between the two groups. Favorable treatment effects were observed only for US patients < 65 years [25].

The effect on chemotherapy-induced neuropathic pain was assessed in a pilot, double-blind, placebo-controlled, crossover trial. The study was proceeded by a sublingually, self-titrating phase to find the optimal dose with the total duration of 4 weeks. No statistically significant difference between the treatment and the placebo groups on the NRS-PI was found [26].

A randomized, dose-response, placebo-controlled trail concluded that the number of patients reporting analgesia significatively differed between placebo and low or medium doses of nabiximol (4, 10 and 16 sprays/day), while the 30% responder rate primary analysis was not significant for treatment groups. Adverse events were dose-related and the low and medium dose group did not differ significatively compared to placebo [27].

One hundred seventy-seven patients with cancer pain inadequate analgesia were randomly assigned to two treatment arms consisting of cannabis extracts and delivered though a pump. Mean doses following the titration phase were maintained during the 2-week treatment phase. Changes from baseline in mean pain NRS were significant for the THC-CBD group but not for THC group. Drug-related adverse events were mild to moderate in severity [28].

Non-neuropathic, non-cancer pain - THC-CBD combination

Fifty-eight patients with rheumatoid arthritis were included in this study, a randomized, placebo-controlled, parallel-group trial. Patients self-administered nabiximol containing fixed doses of THC-CBD for a period of 5 weeks. This was a dose-titration study with a maximum of six actuations allowed, according to individual response. Compared to placebo CBD significatively reduced pain on movement (NRS) and pain at rest. No withdrawals or adverse events were reported for the cannabis-based medicine group [2].

Non-neuropathic, non-cancer pain - THC

A single dose of 8 mg THC (Namisol®) had no effect on pain VAS scores in a group of 56 patients with acute pancreatitis and abdominal pain when compared to active placebo group (diazepam) [29].

In an 8-week study including 50 patients with medical condition related to chronic abdominal pain such as post-surgery and chronic pancreatitis, oral THC (Namisol®) was not

found statistically significant to placebo in pain reduction at the end of treatment [30].

Acute pain - THC

Only one study reported on acute pain. This was a randomized, placebo-controlled, parallel-group study involving 40 women undergoing elective abdominal hysterectomy. During the second postoperative day, after discontinuation of pain medications, participants were administered either THC or placebo in the form of oral capsules (5 mg). Six hours after active treatment, there was no difference in mean VAS scores or summed pain intensity difference scores at movement and rest. There was no difference in the number of adverse events apart from increased awareness of surroundings in the THC group [31].

Non-randomized controlled trials

Neuropathic pain - cannabis-based medicine

Two non-randomized controlled trials assessed the effect of nabiximols, oral spray on neuropathic pain [16, 32]. Nabiximol is a cannabis extract containing fixed doses of THC-CBD, THC or CBD and is delivered though a pump, each actuation delivering 2.7 mg THC and 2.5 mg CBD. Patients self-titrated the optimal dose with 48 actuations allowed in 24 h period. Both studies used a placebo as a control group. The NRS scores differed significantly between control and placebo for the THC and CBD group but not for the extract containing both CBs [16].

Non-controlled trials - cancer pain - nabiximol

Johnson et al conducted a follow-up study (single arm, open label) to investigate the long-term effects and tolerability of cannabis-based medical extract (nabiximol, oral spray) in 43 patients with cancer-related pain and inadequate analgesia [33]. Patients continued taking previous prescribed medication for pain relief. THC and THC/CBD optimal doses were self-titrated during a preliminary phase. Brief pain inventory-short form scores decreased continuously from baseline compared to all time points suggesting an improvement in pain with time. Treatment-related adverse events were dizziness, nausea, vomiting, dry mouth, somnolence and confusion in the THC/CBD group and dizziness, headache and an episode of memory impairment in the THC group. Long-term use was well tolerated, and patients do not increase the dose overtime of other pain-relieving medications.

Experimentally induced pain - THC

Thirty healthy volunteers, marijuana smokers, were recruited in this individually randomized placebo-controlled cross-over trial. Both marijuana strengths (1.98% or 3.56% THC) and high dronabinol dose (20 mg) decreased reported pain compared to placebo. Both dronabinol doses and low strength herbal cannabis increased pain tolerance compared to placebo. However, dronabinol produced a longer-lasting analgesic effect. In addition, dronabinol produced lower ratings of abuse-related subjective effects than smoked cannabis [34].

In a randomized, placebo-controlled, cross-over trial including 15 healthy volunteers, the effect of smoked cannabis with different concentrations (2%, 4% and 8%) was assessed on VAS. Forty-five minutes after the experimental induction of pain, high and medium concentrations of herbal cannabis compared with placebo were effective in reducing capsaicin-induced pain intensity levels [12].

Kraft et al investigated the effect of oral THC capsules (20 mg/once) in 18 healthy females. This was a randomized, placebo-controlled, cross-over trial. The control group was an active placebo receiving diazepam. There was no difference in pain level between THC group and active placebo measured with VAS [35].

Registered clinical trials without results - THC or CBD

Of the registered clinical trials, we identified 30 randomized, controlled trials and five non-controlled trial. Among the controlled clinical trials, 20 were randomized parallel-group and 10 were individually randomized cross-over trials. In the majority of trials, placebo was used as a control group, and only seven trials used an active comparator. The most studied types of pain are neuropathic pain and cancer pain. The most prevalent cannabis product is herbal cannabis (11 trials) with various concentrations of THC, CBD, or both. Route of administration for herbal cannabis is inhalation either smoked or vaporized. Cannabis extract with different concentrations of THC and other CBs apparently non-commercially available were considered in five trials. Nabiximol, a cannabis-based medicine with standardized CBs concentrations, was considered in three trials. Single CBs (THC or CBD) were considered in seven trials; three were non-commercial products while the rest were nabilone, dronabinol and Namisol. Outcome measures varied significantly between trials. Most non-randomized trials were single-arm, open-label with duration varying from 9 days to 6 months and one was an observational study, a prospective cohort. Two assessed the effect of cannabis on neuropathic pain (HIV and chemotherapy-related), two cancer pain and one pain without further specifications. The cannabis products considered for cancer pain were herbal cannabis - inhalation and/or smoked - and cannabis extract and/or oral. For neuropathic pain herbal cannabis either inhalation or vaporized and cannabis-based medical extract - nabiximol, an oromucosal spray, were considered. Pain was assessed with the NRS-PI, VAS and brief pain inventory-short form.

Discussion

Cannabis has been medically deployed for a myriad of conditions, although the majority of trials and scientific literature

cover the indication and effect of cannabis on pain.

In this scoping review, we identified 34 published clinical trials with the majority being controlled trials: 30 randomized controlled trials, three non-randomized trials and one non-controlled trial. The randomized clinical trials were either parallel-group or cross-over trial, the majority used a placebo as a control group and only two used an active placebo group with diazepam [30, 35]. Most studies included more than one treatment arm, e.g., for herbal cannabis different strains with varying concentrations of THC, or single CB extracts and a combination THC-CBD. The cannabis products were in most of the cases used as an adjuvant to current analgesic treatment. A large heterogeneity existed regarding the drugs, doses, routes, frequencies, populations, comparison drugs and outcomes across studies.

The most studied indication within the trials was neuropathic pain in MS patients. In summary, the existing evidence suggests that cannabis is effective for neuropathic pain associated with this condition when cannabis is compared to placebo. The effects of cannabis on neuropathic pain associated with other conditions such as HIV, diabetic pain, post-surgical pain, post trauma and peripheral neuropathic pain were also assessed in a minority of studies, also with promising effects of cannabis for the relief of pain. The effects of herbal cannabis with various concentrations of THC and nabiximols were considered for neuropathic pain in conditions such as central and peripheral neuropathy and post-surgical pain, etc. All studies but one [31] showed a positive effect of cannabis on pain management compared to placebo. Namisol, a cannabis-based medicine containing pure THC derived from a semi-synthetic product, showed improvement in the treatment group when compared to placebo or active control for the treatment of abdominal pain [29, 30].

Two short-term studies (5 days) also assessed the effect of herbal (vaporized and smoked) cannabis in neuropathic pain in HIV patients [9, 10]. Herbal cannabis with different THC concentrations was effective in pain control related to diabetes as reported by two studies [12, 20]. Cancer pain was assessed in three randomized, controlled trial and one non-controlled trial. All studies administered nabiximols in the form of sublingual spray for short-term period of several weeks. Mixed results were provided. Fallon et al (2017) reported primary outcome measure for pain was percent improvement from baseline to the end of treatment in average pain NRS score, the authors found no improvement, and the treatment group performed worse compared to placebo [25].

This review also examined different treatment methods and their effects on various types of pain. Inhaled or smoked THC was investigated in painful sensory neuropathy in HIV patients, in MS and diabetic peripheral neuropathy as well as patients with central and neuropathic pain. These showed good tolerance with minor side effects that increased with the increase in THC dose. The adverse events ranged from minor side effects to psychoactive, euphoria and memory alteration in some patients. THC showed no significant difference from placebo and active placebo groups when it was administered as a single dose oral - Namisol® - in patients with acute pancreatitis and abdominal pain or patients with medical condition related to chronic abdominal pain such as post-surgery and chronic pancreatitis. Dronabinol was found to be more effective than smoking THC as marijuana in decreasing pain sensitivity, and it was associated with less abuse-related effects than smoking.

Combinations of THC and CBD were also reviewed to show significant changes from baseline in pain NRS compared to THC alone. They showed mild to severe adverse events. While nabiximol containing fixed dose of THC and CBD showed more pain control compared to placebo.

Most studies included in this review reported no serious adverse event associated with treatment, although it must be acknowledged that adverse events are not systematically reported. Also, most of the studies reviewed were short-term with one exception that continued for 1 year. A previous systematic review, focusing on the harmful effects of cannabis use, found that 96.6% of the harmful effects of cannabis use are not serious [36]. Another systematic review and meta-analysis suggest that oral and oromucosal routes administration of cannabis-based medicine is more frequently associated with adverse events when compared to inhaled cannabis. Higher THC herbal strains may be more effective for pain control but are also more frequently associated with adverse event. Studying the psychoactive effects of the long-term use of cannabis is highly recommended in order to efficiently weigh the healthcare outcomes of such medication.

The production and commercial application of cannabis products have increased dramatically in the recent decade. In this review, an overwhelming part of the studies employed nabiximols (https://www.gwpharm.com/) as an active administration and studies examining either THC in spray or CBD as oral drop (https://www.eirhealth.com) were sparsely covered. Moreover, a significant number of studies commissioned "self-titrating" regimes, e.g., patients administering the dosage until fit for the individual. The methods covering these self-administration designs were most often unclearly described and dose-effect relationships are warranted. To investigate the effect of dose-response regimes, future studies could preferably include relevant electronic tools such as, MyDosage.com [37], a CBD management application.

Noticeably, we identify a vast number of studies that report a positive effect of CBD and THC, no controlled clinical trials with adequate placebo investigated CBD without THC (being the psychoactive compound). Hence, this remains to be studied although the demand for such is seeing a huge increase projected to be 20 millions USD in sales by 2024 [38]. Recently, it is announced that EirHealth is planning a randomized controlled trial addressing the effect of CBD vs. placebo [39]. A recent promising *in vitro* and murine model study showed promising effects of CBD and significantly decreased pain in the animals [40].

For the clinician, it is noteworthy to consider pros and cons of administering non-steroidal anti-inflammatory drugs (NSAIDs) compared with CBD. NSAIDs are extensively recommended to treat pain and while known to have moderate effect on pain they have also been associated with serious adverse events affecting the gastrointestinal, cardiovascular and renal systems. These very serious and potential lethal complications have not been reported for cannabis products although the effect of cannabis is still to be proven as efficient as NSAIDs. To summarize, cannabis has a highly promising role on the

treatment of chronic pain with an acceptable safety-profile, but still lacks the evidence of the high efficacy of NSAIDs. In future regimes, it is quite likely that cannabis products are to be adjuvant therapy to well-known drugs.

For the clinician, the absorption, metabolism and excretion should be known also for physicians treating patients with severe renal or hepatic disease. Notably, CBs administered through inhalation exhibit similar pharmacokinetics to those administered intravenously and within 3 - 10 min peak plasma concentrations of THC and CBD are observed [41]. Similarly it should be known that the metabolism of both THC and CBS relies primarily on liver function although the fate and activity of the metabolites of CBD are still to be understood. Hence, physicians treating patients with severe liver-malfunction should be careful whereas CBs can be more limply administered to patients with renal disease.

Within the limitations of this review, it can be concluded that there is an available evidence for the effectiveness of THC, CBD or the combination as an adjunct to standard pain medications in patients with refractory MS. More information is needed on drug performance when compared to standard treatment and on an optimal dose for effectiveness and tolerability. There is minor evidence that cannabis and short-term use of inhaled herbal cannabis is effective in the treatment of neuropathic pain for different neurological and orthopedic conditions such as, post-traumatic pain, central and perihelial neuropathy, etc. Limited evidence is available to support the use of cannabis for the treatment of cancer pain mostly in patients with advanced stages of disease. We report promising results within cannabis and rheumatic pain relief.

Supplementary Material

Suppl 1. Characteristics Outcomes and Conclusion of All Included Studies.

Suppl 2. Registered Clinical Trials With No Results.

Acknowledgments

None to declare.

Financial Disclosure

The review was funded by Nordic Cannabis Research Institute (https://www.ncrinstitute.com/).

Conflict of Interest

None to declare.

Author Contributions

RW conducted the search and dataextraction and drafted the first version of the manuscript. RH approved and proofread the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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