



Can cannabidiol (CBD) help with low back pain?

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Abstract

Introduction and Objective. Low back pain (LBP) is a major cause of disability and the main reason why individual patients need medical attention. Pharmacological treatment options for LBP are limited and are often associated with serious side-effects. This makes it necessary to search for new painkillers. One potential therapeutic agent is cannabidiol (CBD). Cannabidiol and tetrahydrocannabinol are the most researched components of cannabis, the plant more commonly known as marijuana or hemp. To the best of our knowledge, this is the first narrative review of the effects of CBD alone on acute and chronic back pain.

Review Methods. Based on the guidelines provided by the Primary Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA), the PubMed/ MEDLINE database was used to identify articles for analysis from the last 30 years. Due to the limited number of studies on this topic, all types of studies that met the inclusion criteria were included. After analysis, 10 studies were included in this review.

Brief description of the state of knowledge. Currently, the use of medical marijuana continues to increase and the Food and Drug Administration (FDA) has already approved four cannabis-based drugs. Cannabidiol (CBD) is a relatively safe substance for humans and generally well tolerated. It is a substance that is easily available and often taken by patients with LBP.

Summary. Evidence for the effectiveness of CBD in the treatment of acute low back pain is lacking. There was only one clinical trial conducted in the Emergency Department that showed no superiority of CBD over placebo in acute LBP. The majority of studies concern chronic rather than acute LBP. Although most of the results suggest a beneficial effect of cannabinoids in relieving chronic LBP, hard evidence is lacking. Rigorous randomized controlled trials are needed.

Key words

low back pain, cannabis, cannabidiol, CBD

INTRODUCTION

Low back pain. Low back pain (LBP) is defined as pain, muscle tension, or stiffness located below the costal edge and above the lower buttock folds, with or without leg pain [1]. LBP is classified in two categories as non-specific or specific due to disc herniation, fractures, osteoporosis, rheumatic diseases, spondyloarthropathy, infections or neoplasms. LBP can also be classified as acute (lasting <6 weeks), sub-acute (lasting from six weeks to three months) or chronic (lasting for more than three months) [1, 2].

According to the World Health Organization (WHO), low back pain is a major cause of disability and the main reason why individual patients need medical attention [3]. Annually, the prevalence of low back pain in the general adult population in the United States is 10–30%, which is also the fifth most common reason for visiting a doctor [4, 5]. Total financial costs related with low back pain in the United States is estimated to exceed \$100 billion a year, two-thirds of it the result of lost earnings and reduced productivity [6].

The first-line drugs in the treatment of back pain are non-opiate analgesics, such as short non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen [7, 8]. Muscle relaxants, such as cyclobenzaprine, are often added.

Systemic glucocorticoids are often used due to the reduction of inflammation; however, taking into account the side-effects of steroids therapy, they cannot be used for a long time [9]. Side-effects of glucocorticoids are common and serious, ranging from acne to Cushing's syndrome, which can be fatal if left untreated [10]. Likewise, due to lack of therapeutic effect numerous physicians use opioids as pain killers. However, pharmacological treatment options for low back pain are limited [11]. This is mainly due to serious side-effects, such as respiratory depression, sedation, and the development of tolerance and addiction [12].

The search for new painkillers is essential and one of the potential therapeutic agents is cannabinoids. Cannabis, the plant more commonly known as marijuana or hemp, (however, the second name has wider meaning than only Cannabis), has been used worldwide for centuries, only the indications for their use have changed [13]. However, the use of cannabis for medicinal purposes is consistent. Cannabis was originally used by the Chinese around 2900 BC and many civilizations have used cannabis to treat a variety of conditions, from joint pain and muscle cramps to gout and malaria [13, 14]. Currently, use of cannabis marijuana in the therapy is steadily increasing as numerous countries all over the world permit the medical use of marijuana [15]. The Food and Drug Administration (FDA) in the USA has approved four cannabis-based drugs: Epidiolex (cannabidiol), Cesamet (nabilone), Marinol (dronabinol) and Syndros (dronabinol) [16]. Often, cannabis is available in pharmacies as a pharmaceutical raw material that patients

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use for vaporization or smoking. Other forms, cannabis-based liquid extracts, oils and pills, are also available.

Cannabis and cannabidiol. According to International Taxonomy Integrated System (ITIS) [17], family Cannabaceae contains 4 genera; one of which is Cannabis L. that contains only one species: Cannabis sativa L. Therefore, all naturally-occurring varieties of cannabis are classified as one species. Cannabis sativa L. contains two subspecies: Cannabis sativa ssp. Indica and Cannabis sativa ssp. sativa. This nomenclature can be confusing, as both the Indica and Sativa subspecies belong to the Cannabis Sativa L species. The multitude of cannabis varieties observed worldwide is due to the ability to interbreed within the species. Current strains contain a different amount of 'indica' and 'sativa' genes, and the one with more genes determines which strain it is classified as, either indica or sativa. That is the reason why, for example, there is the 'Kandy skunk' variety belonging to the Sativa subspecies (containing 65% sativa and 35% indica genes), or 'LA confidential' belonging to the Indica subspecies (containing 100% of indica genes). More than 1,600 chemical compounds have been isolated from C. sativa, of which over 180 are cannabinoids [18].

Besides cannabinoids, various terpenes and phytosterols possess potential pharmacological properties; however, the most studied constituents of cannabis are two cannabinoids: tetrahydrocannabinol (THC) and cannabidiol (CBD) [15, 19]. On the basis of both mentioned cannabinoids, medicinal preparations based on them have been developed and registered. The FDA approved drug, Epidiolex contains > 98% CBD (and less than 0.15% THC). Orally administered it is used to treat two forms of childhood serious epilepsy (Dravet and Lennox-Gastaut syndromes) [16]. It was noticed, that Epidiolex in patients with Dravet syndrome at a dose of 20 mg/kg/day reduces the frequency of epileptic seizures by almost three times, compared to placebo [20]. Similarly, in patients with Lennox-Gastaut syndrome, Epidiolex also reduces seizure frequency [16, 21].

Other drugs approved by the FDA include Cesamet (nabilone; synthetic cannabinoid THC analogue), Marinol and Syndros (dronabinol; (-)-trans- Δ^9 -tetrahydrocannabinol – enantiomer THC form). They are used to treat pain, spasticity, and to reduce nausea and vomiting in cancer patients [16, 22]. Clinical studies with these drugs are presented in Table 1. A pharmaceutical product containing THC and CBD in a ratio of approximately 1:1, in the form of an oral spray is Sativex, which has been approved in Canada and parts of Europe to treat pain and spasticity [23].

Table 1. Completed clinical studies on cannabis preparations

Nabilone	Efficacy in reducing nausea and vomiting in cancer patients	Manera, C. et al.
	Efficacy in the treatment of chronic pain and spasticity associated with multiple sclerosis	
Dronabinol	Analgesic properties in patients with bone metastases from breast cancer	early phase I study: NCT03661892
	Adjunct therapy to opiates in patients with chronic pain	NCT00153192

The use of THC or its analogue in treatment causes psychoactive effects ('high') in patients, which significantly

limits the possibility of its wide use in therapy. A good alternative may be to start therapy with CBD which, although it has different mechanisms of action, can partially cause effects similar to THC, apart from the 'high' effect.

Cannabidiol is a relatively safe substance for humans and generally well tolerated; neither abuse nor dependence has been observed [24, 25]. The most important therapeutic effect of CBD is presented in Table 2 [24, 26, 27, 28]. Additionally, tolerance to CBD does not develop [29]. However, according to studies, it is estimated that up to half of the people taking CBD experienced some side-effects strongly related to CBD dose [30, 31, 32]. In most cases, the side-effects were mild, with dry mouth and fatigue being the most common. [30, 31, 33]. Other side-effects, such as nausea, vomiting, dizziness, agitation, diarrhea and tachycardia, may also occur [30, 31, 33]. The most serious side-effects are pneumonia, respiratory depression and abnormal liver function, which have been found only in children treated for epilepsy [32].

Table 2. Therapeutic effect of CBD

CBD-therapeutic properties	Analgesic	Anti-depressant	immune-modulatory
	anti-nausea anti-cancer	neuroprotective anti-convulsant	anti-oxidant anti-inflammatory

The chemical structure of CBD is shown in Figure 1 [34]. It is synthesized along with other cannabinoids from olivetolic acid, which when combined with geranyl diphosphate (GPP) yields cannabigerolic acid (CBGA) – a common precursor to CBD and THC. Both CBD and THC are synthesized in their acid form (CBDA and THCA) which, when heated, undergoes non-enzymatic decarboxylation to the active forms of CBD (and THC) [35].

The beginning of the 1940s resulted in the discovery and determination of the chemical structure of cannabinoids, including CBD and THC [36]. Although the known mechanisms of CBD action differs from THC, they partially complement each other in action. THC exerts the psychoactive effects and is responsible for potentially intoxicating effects, such as euphoria or a 'high'. Contrary to THC, CBD does not possess psychoactive properties, and additionally acts as antidote for THC poisoning (it decreases the 'high' effect) [26, 37]. CBD is easily available and relatively cheap to produce which makes it a very attractive chemical compound that can be used in medicine.

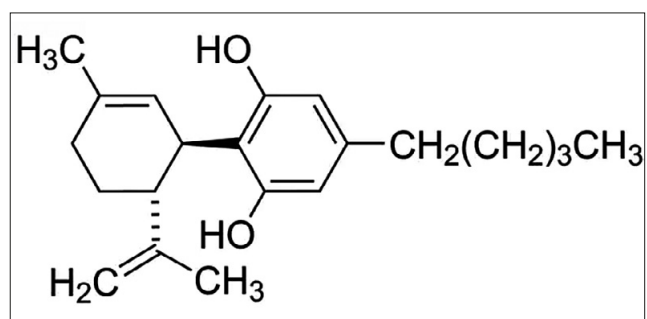


Figure 1. Chemical structure of CBD

Observations to date have shown that CBD exerts a range of actions on the human body, including analgesic as well as anxiolytic, anti-oxidant, anti-inflammatory, anti-convulsant and even anti-psychotic effects [38, 39, 40, 41, 42, 43, 44]. Such a comprehensive interaction is associated with the

involvement of a number of signalling pathways; however, these have not yet been fully identified. Many hypotheses and potential relationships through which cannabinoids may act on the body are available in the literature. Several papers reveal that CBD acts through cannabinoid receptors (CB1 and CB2) which are the part of endocannabinoid system [38, 45, 46, 47], although other receptors may also mediate the biological effects of CBD. These are: G Protein-Coupled Receptor (GPCR) family, serotonergic receptors, opioid receptors, dopamine receptors; CBD can also influence Na⁺, K⁺ and Ca²⁺ ion channels [48, 49, 50, 51, 52].

The aim of this study is to review and assess the impact of cannabidiol on acute and chronic back pain. To the best of our knowledge, this is the first narrative review of the effects of CBD alone on acute and chronic back pain.

MATERIALS AND METHOD

Based on the guidelines provided by the Primary Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA), the PubMed/MEDLINE database was used to identify potential articles for analysis, using the following search terms: 'Cannabidiol', 'CBD', and 'back pain'. The literature search was carried out on 20 February 2023 during which 48 items were retrieved. In the search criteria, articles from 1993 – 2023 were marked. The criteria for inclusion of articles were: studies related to acute and/or chronic back pain, and use of cannabidiol or its derivatives. Exclusion criteria included: other types of pain, chemicals derived from cannabis but not containing cannabidiol and its derivatives, and studies without full access. After careful screening of studies using the above criteria, 10 studies were identified for inclusion. The selection process is illustrated in Figure 2. Because the aim of the review was to produce a comprehensive review of the literature, and due to the limited number of studies on the use of cannabidiol in back pain, the review included all studies that met the inclusion criteria.

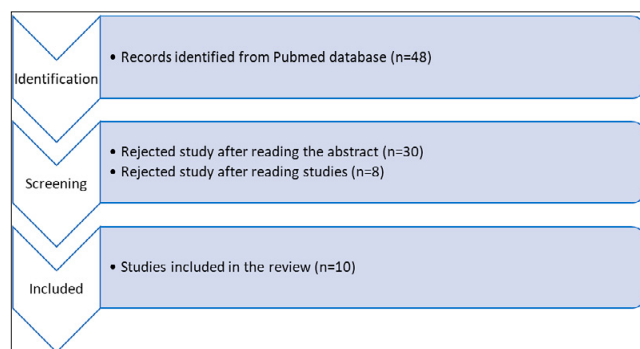


Figure 2. Studies selection process

RESULTS

Table 3 shows all studies included in the review. Due to the fact that different types of studies are included, information about the type of studies is given next to each of them.

DISCUSSION

Acute low back pain. There is a lack of research and evidence on the effectiveness of cannabinoids in acute pain. The only rigorously designed study [53] evaluating the effects of CBD on acute back pain was the CANBACK study [54]. In this clinical trial, 100 participants were enrolled, half of whom received 400 mg CBD and the rest a placebo. After two hours, the level of the pain on a 10-point scale and the length of stay in the Emergency Department (ER) were comparable in both groups. The mean pain scores after two hours and length of stay were 6.2 vs 5.8 and 9.0 vs 8.5 hours, respectively, for CBD vs placebo [54]. The current study, however, has several limitations, including the scale used to assess pain is not objective, there is no information about the drugs taken by the patient before arrival at the ER, and CBD was administered only once [53, 54].

The analyzed studies include a case report of a 40-year-old man who suffered an L3 compression fracture as the result of a fall. After the accident, he rated low back pain on the VAS-8/10 scale. Unsuccessfully treated conservatively with acetaminophen and NSAIDs, he started using CBD cream topically on his lower back and reported a pain reduction of 1–2/10 for about 10 hours. After four weeks, he stopped using the cream and the pain subsided [55].

The effectiveness of cannabinoids in acute pain has been extensively studied in post-operative pain. However, the evidence for the effectiveness of adding cannabinoids in post-operative pain is weak [56]. A recent systematic review and meta-analysis identified eight randomized controlled trials and four observational studies. The authors studied cumulative oral morphine equivalent consumption and rest pain severity at 24 hours post-operatively. As a secondary outcome, they assessed pain at six and 12 hours after surgery, and side-effects related to opioids and cannabinoids, patient satisfaction, and quality of recovery. The authors found no benefit of adding cannabinoids to standard post-operative pain management. The authors also found that the addition of cannabinoids is associated with a signal to increase post-operative pain and hypotension. Therefore, they argue, the obtained results do not support the routine use cannabinoids in the treatment of acute post-operative pain [57]. Cannabis can be used as a supportive therapy after orthopaedic surgery. Cannabis use was associated with reduced pain, increased activity after surgery, and decreased dependence on opioids. In addition, fewer side-effects of marijuana than opioids have been observed. Any effect of cannabis-only use on post-operative pain is not well understood. Therefore, there is a need for randomized controlled trials and prospective studies evaluating the effectiveness of analgesic cannabidiol treatment [58].

Chronic low back pain. The current literature on the effectiveness of cannabidiol in the treatment of chronic low back pain is sparse, but a limited number of studies suggest that it may be an effective alternative to pain management than current drug therapies. The authors of the study found that cannabis can reduce the amount of opioids, as well as improve the quality of life of patients with back pain [58]. In a review by Shah RM et al., the authors cited two studies by Yassin et al. who demonstrated the effectiveness of a cannabis preparation in the treatment of low back pain with fibromyalgia and sciatica. The study used a cannabis preparation with four times the concentration of CBD to

Table 3. Included studies in the review and their conclusions

Study	Type of study	Conclusion
Hayes 2021	Editorial article	CBD is ineffective in treating low back pain. This lack of effect should be acknowledged and the dangers of using CBD should be considered.
Bebee 2021	Randomised, double blinded, placebo-controlled clinical trial	CBD was not superior to placebo as an adjunct medication for relieving acute non-traumatic low back pain in the emergency department.
Eskander 2020	Case series and literature review	CBD transdermal cream has provided patients with significant symptom and pain relief. Further research into the effectiveness of CBD preparations in relieving acute and chronic back pain is warranted.
Shan 2022	Review	The benefits of using cannabis for spinal disorders remain unclear.
Ueberall 2022	Retrospective analysis of anonymized	Nabiximol oromucosal spray was superior and better tolerated than typical oral long-acting opioids in patients with neuropathic back pain.
Lovecchio 2021	Cross-sectional survey	CBD is used by many patients, and further high-quality research on this supplement is essential.
Mondello 2018	Clinical study	THC/CBD agonists may have analgesic properties in spinal cord stimulation patients to treat chronic, refractory pain in failed spinal surgery syndrome
Fitzcharles 2016	Systematic review of randomized controlled trials	There is insufficient evidence to recommend the use of any cannabinoid preparations in the treatment of patients with chronic pain in rheumatic diseases.
Xantus 2021	Review	Observational studies show good results with CBD in reducing low back pain and fear. However, more high-quality studies is needed.
Senderovic 2022	Systematic review	Additional research supporting cannabis use in the older population is warranted.

THC. A group of 31 patients with fibromyalgia and low back pain, and 46 patients with low back pain and sciatica, were included in the studies [59, 60]. Another cited study conducted at a medical centre in California assessed the ability of cannabis to reduce opioid use in patients with LBP [61]. Shah et al., in a literature review concluded that cannabis may be an effective treatment for patients with chronic back pain and spinal cord injuries. However, any risks of long-term use are not well understood [58].

Ueberall M et al., in a retrospective analysis of 1,310 patients, studied the efficacy, safety and tolerability of nabiximol oromucosal spray (NBX), compared to typical oral long-acting opioid (LAO) analgesics in patients with severe neuropathic back pain (NBP). After a six-month study, the superiority analysis of the primary endpoint showed that NBX was superior to LAO: all endpoints measuring pain symptoms and physical function improved significantly with NBX and LAO, with differences favouring NBX ($p < 0.001$). In addition, fewer patients treated with NBX than LAO experienced adverse events (25.5% vs 76.0%; $p < 0.001$), or discontinued treatment due to adverse events (7.9% vs 29.3%; $p < 0.001$) [62]. Hoggart et al. studied the effects of a THC/CBD oromucosal spray used for 38 weeks. The authors found that the use of the spray reduced pain from an average of 6.9 points to 4.2 points on the numerical rating scale. Additionally, the HC / CBD spray was well-tolerated throughout the study and patients did not need to increase the dose over time [63].

A cross-sectional study by Lavecchio et al. confirmed the effectiveness of CBD over a four-week period; an anonymous survey was conducted and the results of 214 patients treated by a spine surgeon at single institution were analyzed. CBD was most commonly used to relieve back pain (66.7%). Additional reported benefits were improved insomnia (25.9%) and improved mood (18.5%). However, 24.1% of patients showed no benefit from CBD [64].

A special type of low back pain is failed back surgery syndrome (FBSS). FBSS is defined by the International Association for the Study of Pain (IASP) as 'a spinal pain of unknown origin either persisting despite surgical intervention or appearing after surgical intervention for

spinal pain originally in the same topographical location' [65]. This type of low back pain can result from persistent inflammatory, neuropathic and compression processes. It is difficult to treat and may not improve with conservative or surgical treatment [66]. Mondaro et al. enrolled 11 people with FBSS who were resistant to pain therapy. The patients were given a combination of THC and CBD, in combination with spinal cord stimulation (SKS). Effective pain control was achieved in all treated patients, and the effect was maintained throughout the treatment period. Pain was rated using a numerical rating scale and decreased from a mean baseline value of 8.18 ± 1.07 to 4.72 ± 0.9 after 12 months of treatment ($p < 0.001$) [67].

Fitzcharles et al. in their systematic review included four randomized controlled trials, of which three trials used nabilone in 71 patients with fibromyalgia, and 30 patients with spine pain. One study used THC/CBD in 58 patients with rheumatoid arthritis. Cannabinoid pain reduction was observed in three included studies; in two, pain reduction was statistically significant ($p=0.02$). Only a comparative study of nabilone vs amitriptyline showed no difference in pain treatment. The authors of the review acknowledge that the risk of bias was high for three studies, and the superiority of cannabinoids over controls was not consistent [68].

Senderovich H et al. in a systematic review cited several studies proving the effectiveness of cannabinoids in the treatment of low back pain in the elderly. Among these studies, there were three RTCs. On the other hand, they cited only four studies, with one meta-analysis not supporting the effectiveness of cannabinoids in the treatment of low back pain. Despite the fact that the study itself had many limitations, the authors concluded that cannabinoids may be an effective treatment for chronic pain. Additionally, the anxiolytic effect of cannabinoids in elderly patients is important as it can reduce the need for opioids and other pharmacological analgesics [69].

The analyzed literature also included a case report of a 61-year-old woman who developed chronic chest dysesthesias after surgical resection of a T6-T7 spinal cord meningioma. After using the CBD cream for seven or eight hours, the symptoms subsided [3].

One review summarized the pharmacological rationale for using CBD to treat back pain. Observational studies suggest that non-psychoactive cannabidiol is a potential effective candidate for pain relief, in addition to which it has a fear-reducing effect, a key factor in pain [70].

Limitations of the Review. The first limitation is the small amount of studies available which examine the effect of CBD alone on low back pain. Only one randomized controlled trial met the inclusion criteria for this review. Most studies analyzed the effects of cannabinoid preparations which, in addition to CBD, also contain THC. This necessitated the inclusion of all types of studies that met the inclusion criteria, which is another limitation of this study. In addition, some of the included studies analyzed the impact of preparations that contained not only CBD.

Low back pain is a very broad term and in the analyzed studies the etiology and duration of pain remained unknown. This could have led to inappropriate choices of studies.

The doses of the tested preparations varied between studies, which also makes it difficult to assess the effectiveness of treatment.

CONCLUSIONS

There is a lack of evidence for the effectiveness of CBD in the treatment of acute LBP. The only available clinical trial examining the effects of cannabidiol in patients treated in the Emergency Department showed no superiority of CBD over placebo. Similarly, in the treatment of post-operative pain, adding cannabinoids to standard pain therapy showed no benefit. In the presented literature, there were only two case reports confirming the effectiveness of CBD in the form of a topical cream. Rigorous randomized controlled trials are needed to evaluate the effectiveness of CBD in the treatment of acute low back pain.

There are more studies on the use of cannabinoids in the treatment of chronic LBP than acute pain. Although most of the results suggest a beneficial effect of cannabinoids in relieving chronic low back pain, hard evidence is lacking. Almost all of the studies reviewed involved CBD and THC preparations. In the analyzed literature, there were only case reports confirming the effectiveness of using only the preparation with CBD in the form of a cream. As with acute pain, further research is needed.

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