

Żyga Justyna. A review of studies evaluating medical cannabis for the chronic pain management. *Journal of Education, Health and Sport*. 2022;12(8):250-256. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2022.12.08.024>  
<https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.08.024>  
<https://zenodo.org/record/6953815>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.

Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.  
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 17.07.2022. Revised: 27.07.2022. Accepted: 02.08.2022.

## A review of studies evaluating medical cannabis for the chronic pain management

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### Abstract

**Introduction:** Medical cannabis for patients with chronic pain related to various conditions has been the focus of numerous investigations. Cannabis-based medicine has been described for hundreds of years but only recently have we seen the more scientific, evidence-based approach to its use, and ongoing investigations continue to explore its potential medical benefits.

**State of knowledge:** As the results of studies assessing medical cannabis in pain alleviate seem promising, only weak recommendations are available. Important factors to consider in the development of guidelines include optimal doses, routes of administration and used types of cannabinoids. In discussed studies no serious adverse events were reported and treatment was well tolerated by participants.

**Conclusions:** Evidence suggests that cannabis-based medicine can be safe and effective in pain relief. Further high-quality randomised clinical trial studies are needed. It is important to assess the safety profile of each individual cannabinoid formulation and define the population that can benefit from cannabis therapy for establishment of prospective recommendations and guidelines.

**Keywords:** Cannabis; endocannabinoids; Δ9-tetrahydrocannabinol; cannabidiol; chronic pain

### Introduction

Cannabis-based medicine has been described for hundreds of years but only recently have we seen the more scientific, evidence-based approach to its use, and ongoing investigations continue to explore its potential medical benefits. Medical cannabis is increasingly used to manage pain, with limited understanding of their efficacy and safety. The use for medicinal purposes, dates back over 5000 years, has been documented in the world's oldest pharmacopodia, the Chinese pen-ts'ao ching, and in Indian Ayurvedic medicine for neuralgia, headache, toothache, and other maladies as early as 1000 B.C [1].

### **The endocannabinoid system**

Cannabis contains over 450 compounds, with at least 70 classified as phytocannabinoids. *Cannabis sativa* plant is rich in two cannabinoids of particular medical concern - delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Their isolation from the cannabis plant, and the discovery of the endocannabinoid system has sparked interest in how it regulates homeostatic functions. The endocannabinoid system plays an active role in controlling pain and animal models were employed to support this hypothesis. It operates via multiple mechanisms involving neuromodulation and immunomodulation at peripheral, spinal, and supraspinal levels. The endocannabinoid system consists of endogenous cannabinoids, their receptors and the enzymes responsible for their synthesis, regulation, transport, and metabolism. Three types of cannabinoids are recognized in the literature: phytocannabinoids derived from the cannabis plant, synthetic and endogenous cannabinoids, such as anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol, produced by the body [2, 3].

Cannabinoid-based medicines act on the human endocannabinoid system, a network of cannabinoid receptors type 1 and 2 (CB1 and CB2 receptors), and other receptors distributed throughout the body. CB1 receptors are congregated predominantly in the central and peripheral nervous systems, with a low concentration in the respiratory centre in the brainstem, while CB2 receptors are found largely in the immune and hematopoietic systems, as well as the brain, liver, endocrine pancreas, and bone [4]. Cannabis exerts its action via its two major active components, THC and CBD. The more active ingredient in cannabis, THC, is responsible for the euphoric effects associated with cannabis. However, THC evokes side effects, such as fear and tachycardia, limiting its therapeutic potential, but some studies found that CBD reduced intense experiences of anxiety or psychosis-like effects of THC. CBD was found to exert beneficial effects in chronic pain, fear, anxiety and epilepsy, autoimmunity, cardiovascular and kidney diseases [4, 5]. Despite a wide range of potential favourable action of CBD, the safety of its use cannot currently be established [6].

### **Therapeutic ways for the management of chronic pain**

Chronic pain, defined as pain persisting or recurring for three months, has been recognised as a major cause of disability globally. Approximately 20% of the population in North America, Australia, and Europe report chronic pain. It is more common among women, elderly people, veterans, indigenous populations and the socioeconomically disadvantaged. The prevalence of chronic pain of any type among middle and low income countries reaches 33% [7].

Pain management is important to obtain a better quality of patient's life. The assessment of pain usually includes a visual analogue scale from 0 to 10, where the lowest value indicates no pain and the highest indicates the worst possible. In most studies, a clinically significant improvement in pain intensity is defined as a reduction of 2 points. Patients with chronic diseases may face unbearable pain on a daily basis and require more potent analgesics and their more frequent administration. The chronic pain may cause fatigue, sleep disturbance and mood disorders which can seriously impact the patient's quality of life [8]. Mild pain is generally managed with first-choice analgesics such as paracetamol, non-steroid anti-inflammatory drugs and cyclooxygenase inhibitors. Opioids are often the choice of analgesic in chronic pain management. They are generally used for cancer-related pain, acute surgical and post-traumatic pain. Long-term use may result in the development of tolerance, in which progressively higher doses are required to achieve the same pharmacological outcome.

Antidepressants indicated in the use of chronic pain include tricyclic antidepressants (TCAs), and serotonin and norepinephrine reuptake inhibitors (SNRIs) that provide pain relief separate from their antidepressant effects. Moreover, anticonvulsants are successfully used for chronic neuropathic pain, including trigeminal neuralgia [8, 9].

### **Methods of research**

A literature search of the PubMed database was carried out for clinical trials assessing medical cannabis use in pain alleviation. Papers from the last 5 years were taken into account. Reviews

and articles about non-medical use have been excluded. The key search terms used were “medical cannabis”, “medical use”, “chronic pain”, “clinical trials”.

### **State of knowledge**

There are 8 publications assessing the efficacy of medical cannabis use in pain relief. Subject number varies from 20 to 100. Participants experiencing chronic pain due to various conditions, defined more or less specifically: fibromyalgia, cancer, abdominal pain, sickle cell disease, neuropathy, low back pain. The most popular route of administration was inhalation of cannabis or its active components, but oral and topical use have also been investigated.

An experimental, randomised study by Van de Donk et al. explored the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. No effect greater than placebo was obtained, although more subjects receiving Bediol (6.3% THC, 8% CBD) displayed a 30% decrease in pain scores compared to placebo (90% vs 55% of patients), with spontaneous pain scores correlating with the magnitude of drug high. Cannabis varieties containing THC caused a significant increase in pressure pain threshold relative to placebo. Cannabidiol inhalation increased THC plasma concentrations, but diminished THC-induced analgesic effects. This phenomenon indicates synergistic pharmacokinetic but antagonistic pharmacodynamic interactions of THC and CBD. The experimental trial shows the complex behaviour of inhaled cannabinoids with inconsiderable analgesic responses. Further studies are needed to determine long-term treatment effects on spontaneous pain scores, THC and CBD interactions, and the role of psychotropic symptoms on pain relief [10].

Almog et al. performed a study evaluating the pharmacokinetics, analgesic effect, cognitive performance and safety of cannabis treatment with precise dosing. Both doses (0,5mg and 1mg of THC), but not the placebo, demonstrated a significant reduction in pain intensity compared with baseline - 63.64% of the patients in 0,5mg dose, and 69.57% of the patients in 1mg dose demonstrated at least 2-points reduction in pain Visual Analogue Scale score. Adverse events were mostly mild and there was no evidence of consistent impairments in cognitive performance. Evidence suggests that cannabis-based medicine can be safe and effective in pain relief - given that participants presented chronic conditions, further long-term studies are needed [11].

Opioids are widely prescribed for chronic pain, but in clinical practice it is recommended to delay or prevent the initiation of treatment with opioid analgesics, decrease the duration of treatment, reduce the dosage and adverse outcomes, without causing an unacceptable increase in pain. There is substantial interest in the opioid-sparing potential of cannabinoids in the context of pain management - cannabinoid co-administration may enable reduced opioid doses for analgesia, what was supported by results of preclinical and observational studies [12]. The trial performed by Zylla et al. of early and delayed start medical cannabis also suggest that cannabis may improve pain management and minimise opioid utilisation. As the sample size was small and no placebo group took part in the investigation, authors point to the need for larger, prospective trials. The identification of optimal doses and populations who may experience benefits with cannabinoids may enable elaboration of appropriate recommendations [13].

Sickle cell disease is characterised by chronic pain and episodic acute pain caused by vasoocclusive crises, often requiring high doses of opioids for prolonged periods. Abrams et al. aimed to determine whether inhaled cannabis is more effective than placebo in relieving chronic pain related to this condition. Authors define cannabis inhalations as safe and well tolerated. Inhaled cannabis was more effective than placebo in interference in mood, but there was no statistically significant difference in pain rating between cannabis and placebo. These findings suggest that cannabis should be investigated further in larger and longer clinical trials in adults with sickle cell disease with chronic pain as an adjunct or alternative to opioids [14]. Similar

outcome was obtained in a study of 65 patients with abdominal pain - no difference in pain relief between a THC and a placebo pill in patients with chronic abdominal pain was found. Nevertheless applied treatment was safe and well-tolerated during a 50-day to 52-day period [15].

Another observational study (Yassin et al.) aimed to assess the improvement in function and pain relief associated with medical cannabis therapy in patients with low back pain related to fibromyalgia. The addition of medical cannabis to the standardised analgesic therapy allowed an significant improvement in all participants at 3 months after initiation and was maintained at 6 months. Similar results refer to the range of motion in the lumbar region.

This observational study demonstrates an advantage of medical cannabis therapy in patients with low back pain related to fibromyalgia as compared with standardised analgesic therapy. Authors highlight the need for further randomised clinical trial studies that should assess medical cannabis therapy in fibromyalgia, as the current study limitations include the lack of standardisation of the amount of the consumption of THC and CBD [16].

Cannabidiol (CBD) is the major non-psychoactive phytocannabinoid. Unlike most cannabinoids, including THC, CBD does not have psychomotor or cognitive effects. CBD has attracted increasing medical interest because of its anxiolytic, anti-inflammatory, anti-emetic, anti-epileptic and anti-psychotic effects. It has been approved in several countries for the treatment of neuropathic pain. The objective of the study conducted by Bebee et al. was to evaluate the analgesic effect and safety of single oral administration of CBD for patients with low back pain. Study found no evidence of benefit for patients with acute low back pain; the CBD and placebo groups did not differ with respect to hospital length of stay, adverse effects, and additional opioid medication use [17].

Results of study performed by Xu suggest that the transdermal application of CBD oil can achieve significant improvement in pain and other disturbing sensations in patients with peripheral neuropathy. The treatment product was well tolerated and may provide a more effective alternative compared to other current therapies in the treatment of peripheral neuropathy. No adverse events were reported [18].

Table 1: Comparison of studies assessing efficiency of medical cannabis in pain relief; first author and publication year was mentioned

| Study            | Number of subject + aetiology | Intervention  | Results   |
|------------------|-------------------------------|---|---|
| Van de Donk 2019 | 20x fibromyalgia              | Herbal Cannabis: Bedrocan® (22% THC, < 1% CBD); Bediol® (6.3% THC, 8% CBD); Bedrolite® (9% CBD, <1% THC) inhalation | None of the treatments were more effective than placebo. Bediol® group displayed a 30% decrease in pain scores compared to placebo with pain scores correlating with the magnitude of drug high |
| Almog 2020       | 25x chronic pain              | THC 1mg, THC 0,5mg, precise dose inhalation of Bedrocan® (22% THC, <1% CBD)   | Demonstration of analgesic effect with the largest effect in the 1mg dose group   |
| Zylla 2021       | 30x stage IV                  | dose of 30–40mg of THC  | Mean pain scores remained   |

|               |                                   |   |   |
|---------------|-----------------------------------|---|---|
|               | cancer requiring opioids          | and 30–40mg of CBD, comparing early cannabis (EC) to delayed start cannabis (DC). Inhalation, oral, topical | similar between the two groups, but an increase in opioid dose in a group that received delayed cannabis                  |
| De Vries 2017 | 65x chronic abdominal pain        | 8mg THC tablets (full-dose and increasing)  | No difference between a THC tablet and a placebo tablet in reducing pain measures in patients with chronic abdominal pain |
| Abrams 2020   | 23x sickle cell disease           | 4.4% THC and 4.9% CBD inhalation  | No significant difference in pain rating assessment   |
| Yassin 2019   | 31x low back pain in fibromyalgia | THC:CBD (1:4 ratio) inhalation  | Clinically significant reduction in pain at 3 months  |
| Xu 2020       | 29x peripheral neuropathy         | CBD topical cream   | Significant improvement in pain and other disturbing sensations in patients with peripheral neuropathy                    |
| Bebee 2021    | 100x low back pain                | 400mg CBD oral solution   | CBD was not superior to placebo as an adjunct medication for relieving low back pain                                      |

Medical cannabis for patients with chronic pain related to various conditions has been the focus of numerous investigations. Reviewed studies have not shown deaths or life-threatening side effects associated with the use of cannabis. Only weak recommendations are available for cannabis in patients with chronic pain, considering it as a third- or fourth-line therapy. Important factors to consider in the development of guidelines include optimal doses, routes of administration and used types of cannabinoids. The development of reliable recommendations for medical cannabis use will require well-designed and large randomised control trials with long-term follow-up. The effects of cannabinoids and their interaction in the body are yet to be fully understood, furthermore the potential benefits of cannabis-based medicine might be outweighed by their potential harms. However the therapeutic effects of some cannabinoid derivatives are already approved for the management of chronic pain and other conditions in some countries [19].

### **Online information about medical cannabis**

People suffering from chronic pain are looking for alternative treatment methods often using the internet, but the information that can be found online is not always aligned in terms of the therapeutic areas. The therapeutic area most frequently mentioned on the Web is pain. In the United Kingdom, The National Institute for Health and Care Excellence guidelines specifically recommend not to prescribe cannabis products for chronic pain unless as part of a clinical trial and pain treatment is not an approved indication for any cannabis product in the United States as of February 2020. Another indication frequently mentioned were multiple sclerosis, epilepsy, cancer and psychiatric disorders. As indication for Dravet and Lennox-Gastaut Syndromes is approved, in other conditions the evidence is low or moderate, often failing to show superiority

as compared to conventional drugs. Only 22% of webpages report potential side effects with a large variability - side effects were mentioned more frequently by health portals and non-profit organisations and much less frequently by commercial websites and news outlets, thus suggesting a bias associated with commercial interests and newsworthiness. It could raise unrealistic expectations in the public and contribute to a hype that could potentially lead patients to use cannabis-based products as self-medication in case of absence of medical prescription for indications without strong evidence of efficacy. In addition, self-initiated use may lead to side effects and drug interactions [20].

### **Safety profile of THC and CBD**

In discussed studies concerning pain treatment no serious adverse events were reported. Across other clinical trials, the most common adverse events reported by patients receiving THC were generally dizziness, drowsiness and fatigue, dry mouth, nausea, vomiting, and effects on cognitive function (such as perception disorders, euphoria, confusion). Balance and coordination problems were also commonly reported. The profile of CBD is different to THC, with common adverse events including diarrhoea, somnolence, pyrexia, decreased appetite, vomiting, upper respiratory tract infection, and breakthrough epilepsy symptoms. The most notable serious event was elevated liver enzymes. Overall analysis of traditional measures of drug safety, such as number and type of adverse events, is challenging for cannabinoid-based medicines given the substantial differences between cannabinoids, individual product composition, study designs, indications and populations studied [21].

### **Summary**

The number of clinical studies assessing the potential therapeutic benefits of cannabinoids is increasing, especially as cultural and legal barriers to research and access continue to ease. Numerous knowledge gaps exist across many aspects of cannabinoid research. Analysis of the safety of cannabinoid-based medicine is challenging due to disparities in formulation, dosing, administration method, indication, and confusion with recreational cannabis use. Further high-quality studies are needed to establish the safety profile of each individual cannabinoid formulation and define the population that can benefit from cannabis therapy.

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