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Medical Cannabis in the Pharmacological Treatment of Fibromyalgia Narrative Review

Rangel-Jaimes GW[1], Ortega-Agón KA[1] and González-Maldonado JF[2]*

[1]Interventional Pain Management and Palliative Care, Clínica ALIVIAR - FOSCAL, Colombia

[2]Department of Anesthesiology, Universidad Autónoma de Bucaramanga (UNAB) - Clínica FOSCAL Internacional, Colombia

***Corresponding author:** Julián Felipe González-Maldonado, 2Department of Anesthesiology, Universidad Autónoma de Bucaramanga (UNAB) - Clínica FOSCAL Internacional, Floridablanca, Colombia, Tel: 57 7 679 83 58; Email: pipegoma87@hotmail.com

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Abstract

Introduction: Fibromyalgia is one of the most frequent pain syndromes, and constitutes a real therapeutic challenge, for which a multimodal and multidisciplinary approach is necessary. In recent years, expectations have grown regarding the possible efficacy of cannabis as part of the adjunctive management in this pathology.

Objective: Prepare a narrative review regarding the evidence that exists on the safety and efficacy of medicinal cannabis in the pharmacological management of fibromyalgia.

Methods: A research was carried out on the scientific evidence available in databases (Pubmed/ Medline, Science Direct, Scielo, Cochrane, BioMed Central) using the terms "(cannabis OR cannabinoids) AND fibromyalgia", to develop a narrative review of the literature.

Results: The initial search resulted in a total of 144 titles. After the exclusion process, only 11 articles were relevant for the narrative review of this article.

Conclusion: Despite the promising evidence, more research is needed to determine the clinical benefits, the required dose, the ideal route of administration and composition, and the tolerability profiles of the different cannabinoids in the management of fibromyalgia.

Keywords: Cannabis; Fibromyalgia; Cannabinoids; Cannabidiol; CBD; Tetrahidrocannabinol; THC

Abbreviations: THC: Tetrahydrocannabinol; VAS: Visual Analog Scale; FIQ: Fibromyalgia Impact Questionnaire; FIQR: Fibromyalgia Impact Questionnaire Revised; FAS: Fibromyalgia Assessment Scale; PSQI: Pittsburgh Sleep Quality Index.

What do we know about this problem?

- Fibromyalgia is a very common pain syndrome in which the available therapeutic options are not completely effective.
- In recent years, several studies have been published evaluating the use of medical cannabis in the treatment of fibromyalgia.
- The evidence regarding the safety and efficacy of medical cannabis in this condition is not conclusive.

What is the new contribution of this study?

- This article makes a detailed review of all the original studies published to date in the databases reviewed, allowing to identify the main limitations in the design of these studies that have prevented conclusive results on the use of medicinal cannabis in treatment of

fibromyalgia.

Introduction

Fibromyalgia is one of the most frequent pain syndromes, after osteoarthrosis, it is the second most prevalent rheumatological entity, it predominates in young women [1,2], and its main manifestations are diffuse musculoskeletal pain, morning stiffness, fatigue, sleep disturbances and frame of mind [1,3]. It generally has concomitant histories of headaches, temporomandibular joint disorders, chronic fatigue, irritable bowel syndrome, gastrointestinal disorders, endometriosis, interstitial cystitis, and generalized muscle pain, mainly in the cervical and dorso-lumbar regions [3-7].

Because of its multiple manifestations, and the psychological, behavioral, and social problems that influence its pathogenesis, fibromyalgia constitutes a real therapeutic challenge; this requires a multimodal and multidisciplinary approach, always including pharmacological and non-pharmacological strategies [1]. Among the pharmacological options, we have serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, gabapentinoids [8-10]. However, these medications may fail because they are not tolerated by the patient, or they may not be completely effective in returning to their previous quality of life [11,12].

Cannabis has recently been included in the treatment of diseases such as multiple sclerosis, some types of refractory epilepsies, Parkinson's disease, chronic neuropathic pain, among others [13-15]. Although there are few studies evaluating its usefulness in fibromyalgia, in recent years the expectation has grown regarding its possible efficacy as part of adjunctive management. For this reason, literature was searched in different databases, with the aim of reviewing the existing evidence on medical cannabis in the treatment of fibromyalgia.

Methods

For the literature search, the databases of Pubmed/ Medline, Science Direct, Scielo, Cochrane, Biomed Central were used. The search was carried out in June 2020 using the terms "(cannabis OR cannabinoids) AND fibromyalgia". The search for articles was carried out independently. For the narrative review, the following inclusion criteria were defined: 1) Systematic reviews, clinical trials, observational and descriptive studies; 2) Studies in English and Spanish; 3) There was not limit for the date of publication; 4) All cannabis preparations were included.

Results

The initial search resulted in a total of 144 titles. The exclusion of duplicate articles and types of studies other than systematic reviews, clinical trials, observational studies, and descriptive studies, resulted in 31 studies. Abstracts were screened by all authors for relevance to the review topic. After eliminating all the articles that made reference to other aspects irrelevant to the review topic, and after eliminating the studies in languages other than English and Spanish; only 11 studies were suitable for the review of this article (Figure 1).

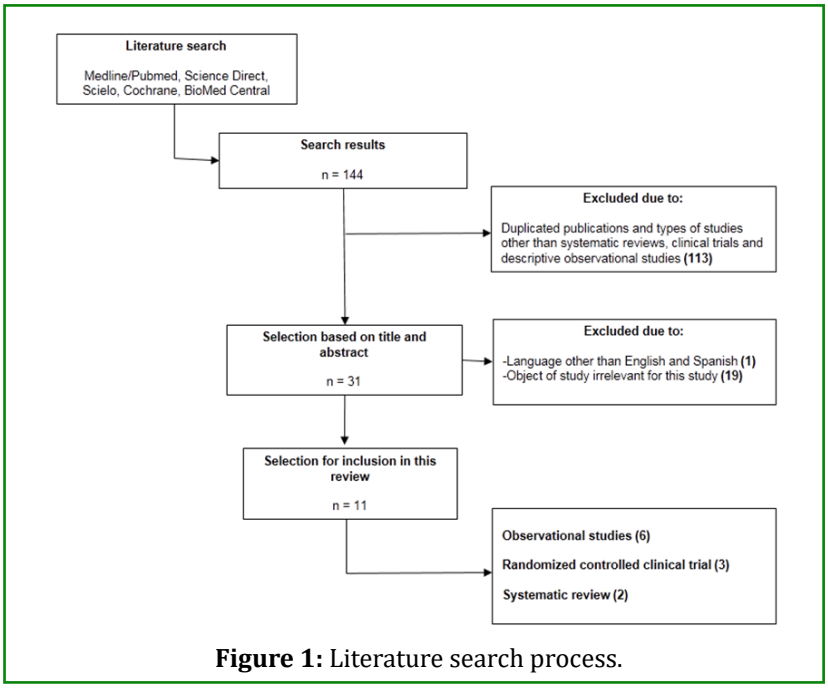

Figure 1: Literature search process.

Discussion

Medical cannabis overview

Cannabinoids in the human body act on a complex internal system known as the Endocannabinoid System, which performs homeostatic functions in multiple systems due to the presence of two isotypes of cannabinoid receptors (CB1 y CB2), These are located in multiple organs and tissues of the human body, such as the central nervous, digestive, cardiovascular, genitourinary, musculoskeletal, immunological and integumentary systems [16-18]. In this way, it regulates various physiological processes, including those related to appetite, mood, temperature control, modulation of nausea, cell migration, control of inflammation and modulation of pain. Hence, the growing interest in studying the therapeutic potential of medicinal cannabis [19-22].

The use of cannabis in multiple pathologies dates back many years, the medicinal properties of cannabis were known and used in ancient China, and historical records tell us of its use more than 4,000 years ago [19,20]. However, in recent years, with the description of the endocannabinoid system at the molecular level and with advances in the legislation of several countries that allows the prescription of medical cannabis in certain cases, research on the use of cannabis in multiple pathologies has increased [21,22].

There are three recognized types of cannabinoids:

Phytocannabinoids: They are derived from the cannabis plant, the best known of this subgroup are THC (tetrahydrocannabinol) and CBD (cannabidiol) [23-25].

Synthetic cannabinoids: they are based on the chemical structure of THC or other ligands that bind to cannabinoid receptors.

Endogenous cannabinoids or endocannabinoids, such as anandamide (AEA) and 2- arachidonoylglycerol (2-AG), found in animals, whose basic functions regulate the physiology of various activities of living beings such as eating, sleeping, the response to stress, the regulation of pain pathways or thermoregulation.

The cannabis sativa plant contains approximately 400 different chemical compounds, of which about 60 to 100 are considered within the group of cannabinoids. The main responsible for the psychoactive properties corresponds to THC, which through its action at the level of the CB1 and CB2 receptors affects pain, appetite, orientation, and emotions. CBD has analgesic, anti-inflammatory and anxiolytic properties, acting as a negative allosteric modulator of the CB1 receptor. The relative ratio of THC: CBD determines the type of effect, the pharmacokinetics and the adverse effects of each compound [26].

Other components can contribute to the total effect of cannabis among them we find terpenoids and flavonoids. The former share a common precursor with phytocannabinoids and are responsible for giving cannabis its distinctive aroma, they also induce mainly anti-inflammatory medicinal effects and have modulating effects on THC. Flavonoids, meanwhile, have shown antiarthritic effects in mice studies [27-29].

Evidence for medical cannabis in Fibromyalgia

One of the possible pathophysiological mechanisms involved in the origin and perpetuation of fibromyalgia is the deficiency of the endocannabinoid system [30]. This theory was exposed for the first time in 2001 and talks about the relationship that exists between the reduction in the function of the endocannabinoid system and the triggering of alterations such as: decreased pain threshold, and disorders in digestion, mood and sleep [30,31]. As mentioned previously, the endocannabinoid system is responsible for regulating a large part of the physiological functions of humans and animals, therefore, a variation in its adequate levels can generate alterations in homeostasis and consequently diseases [16,18,21,22,30]. Recently, it has been observed that both fibromyalgia and migraine are associated with hyperalgesia secondary to central endocannabinoid hypofunction [30].

In the last two decades, medical cannabis has gained great media, socioeconomic and scientific relevance; becoming a subject of debate, regulation and evaluation [26,28,32,33]. As the use of medical cannabis increases, discussions about the impact it will have on individuals and society are vehement [34]. Many countries are under public pressure to change their internal policies and establish legalization plans for recreational and medicinal purposes [35,36].

Meanwhile, a significant number of patients use products that have not had rigorous clinical studies, whose composition and quality have not been evaluated, that have indications based on insufficient or weak evidence, and with demonstrated effectiveness that is barely acceptable. Next, the studies published in the literature that have addressed the use of medicinal cannabis in the management of fibromyalgia are reviewed.

Synthetic Cannabinoids and Fibromyalgia

The synthetic cannabinoid studied in fibromyalgia corresponds to nabilone, an analog of tetrahydrocannabinol (THC), the main psychoactive compound found naturally

in cannabis. In 2008, a randomized, double-blind, placebo-controlled study was published to determine the benefit of nabilone in treating pain and improving quality of life in 40 patients with fibromyalgia.

Patients received titration with nabilone or placebo. In the second and fourth weeks, the following were evaluated: the visual analog scale (VAS) for pain, the number of tender points, the average pain threshold of tender points and the Fibromyalgia Impact Questionnaire (FIQ). There was a significant decrease in pain and anxiety in the nabilone group at 4 weeks, compared to the placebo group. The treatment group experienced more side effects, although the latter were mild [37].

Two years later a new randomized, double-blind study that sought to compare nabilone with amitriptyline in patients with fibromyalgia and chronic insomnia was published. It included 31 patients, of whom 29 completed the trial. Although sleep improved with both amitriptyline and nabilone, the latter was superior to amitriptyline. However, neither group had effects on pain, mood, or quality of life. Adverse effects were mostly mild to moderate [38].

The two previous studies were included in the Cochrane review published in 2016, where it was considered that there was no convincing, unbiased and high-quality evidence to suggest that nabilone is valuable in the treatment of patients with fibromyalgia [39]. It should be noted that the population studied in the two previously mentioned studies was small and the follow-up of the patients was short-term, which limits the quality of the evidence.

Phytocannabinoids and Fibromyalgia

In 2011, Fiz, et al. published a study that aimed to describe the patterns of cannabis use and the benefits associated with its use in patients with fibromyalgia; 56 patients were included, 28 of them were cannabis users and 28 were non-users. Information on medical cannabis use was recorded in a specific questionnaire the perceived benefits of cannabis use were recorded using the visual analog scale (VAS). Cannabis users mentioned different forms of administration: smoked (54%), oral (46%) and combined (43%). The amount and frequency of cannabis use were variable. After 2 hours of cannabis use, VAS scores showed a statistically significant reduction in pain and stiffness, improved relaxation, and increased drowsiness and a sense of well-being [40]. It is highlighted in this study that the diagnosis of fibromyalgia met the criteria of the American College of Rheumatology. On the other hand, it has several limitations: there is a selection bias because most of the patients in the cannabis group were recruited from a cannabis association; the sample size is small, and there is also variability in the routes of administration, quantity and frequency of cannabis use.

Yassin, et al. conducted an observational study in 2017 in which 31 patients were included; this study evaluated the possible improvement, in terms of pain and functionality, associated with the start of treatment with medical cannabis in patients with fibromyalgia and low back pain. The patients had been previously treated with opioids as needed, plus duloxetine for at least 3 months; subsequently, management with medicinal cannabis was started after the request and approval of the patient. The recommended treatment with medical cannabis was 1: 4 THC-CBD, with THC levels less than 5%, patients treated with medical cannabis were followed for a minimum of 6 months, finding improvement in pain and functionality both at 3 and 6 months [41]. The main limitation of this study is the population number, as well as the lack of questions about previous cannabis use. It is noteworthy that this study, contrary to others published regarding the use of cannabis for pain relief, it does specify the dose used, the route of administration (vaporized or smoked) and the percentage of THC handled, although it does not specify the strain of cannabis.

Subsequently, a retrospective analysis published in 2018 by Habib, et al. aimed to examine the effects of medical cannabis on fibromyalgia patients in an Israeli population. 26 patients were included, 73% were women, the mean dose of medical cannabis was 26 ± 8.3 g per month, and the mean duration of medical cannabis use was 10.4 ± 11.3 months. All patients reported significant improvement on the Fibromyalgia Impact Questionnaire Revised (FIQR), and half of the patients stopped taking any other fibromyalgia medications. Eight patients (30%) experienced very mild adverse effects [42]. It is worth noting that in this study all the patients included met the criteria for fibromyalgia. Although the additional pain relievers taken during the study and two months prior to the study were taken into account, it did not inquire about the use of cannabinoids in the past. Another limitation of this study is its retrospective nature, since the questionnaires were carried out long after the start of cannabinoid medication, although mostly before 3 months [42].

This same year Habib et al, published a study that sought to report on cannabis use habits among fibromyalgia patients in Israel. A questionnaire was published in three large fibromyalgia Facebook groups in that country. The questionnaire contained anonymous questions where, among other things, the effect of cannabis on pain, sleep, depression and anxiety was evaluated; adverse effects of cannabis; feelings of cannabis dependence and medical cannabis license. Out of 2705 people, 383 (14%) responded to the questionnaire. Of those surveyed, 84% reported using

cannabis, 44% were licensed for medical cannabis, 80% of cannabis users smoked pure cannabis or cannabis mixed with tobacco. 94% reported pain relief, while 93% reported better sleep quality, 87% an improvement in depression, and 62% an improvement in anxiety. Only 8% reported cannabis dependence [43]. However, this study has important limitations: the strain of cannabis used was not reported, it did not inquire about the use of cannabis in the past, it did not request information about the concomitant use of other medications, the questionnaires applied were not validated, they did not establish a confirmation of the diagnosis of fibromyalgia in patients.

On the other hand Sagy, et al. designed a prospective observational study [44], in which they followed up 367 patients for a period of six months from 2015 to 2017 to evaluate the safety and efficacy of medicinal cannabis in fibromyalgia. A gradual titration process with cannabis rich in THC was defined and both the oral route of administration and the inflorescence were used. The authors found that the intensity of pain was significantly reduced, and there was also an improvement in quality of life and symptoms related to fibromyalgia, with the appearance of mild adverse effects [44]. From this study, it is important to highlight that it has a long cohort of patients, they were followed for a period of 6 months, and that the effect of medicinal cannabis on all aspects of fibromyalgia was studied: improvement in chronic pain, quality of life, perception of the disease, specific symptoms and incidence of adverse effects. However, we must point out that, given its observational nature, it has limitations, which is why it cannot clearly establish causality between cannabis and improved outcomes. Furthermore, 14 different strains of cannabis were used, which prevents a comparison between them and therefore no recommendations can be given in terms of effectiveness and safety.

Subsequently, van de Donk, et al. in 2019 published a randomized placebo-controlled study in which 20 patients with chronic pain diagnosed with fibromyalgia were included [45]. 4 different varieties of cannabis were tested with the exact knowledge of the THC and CBD ratios, Bedrocan (22.4 mg THC; <1 mg CBD); Bediol (13.4 mg THC; 17.8 mg CBD); Bedrolite (18.4 mg CBD; <1 mg THC) and a placebo variety without THC or CBD. After administration by vaporization of the entire preparation, plasma concentrations of THC and CBD, electrical and pressure pain thresholds, and spontaneous pain scores were measured for 3 hours. Neither treatment had a greater effect than placebo on spontaneous or electrical responses to pain, although more subjects who received Bediol showed a 30% decrease in spontaneous pain scores compared to placebo (90% vs. 55% of patients, $p = 0.01$); spontaneous pain scores correlated with psychoactive effects, which were mild to moderate with Bedrocan and Bediol. THC-containing cannabis strains caused a significant increase in pressure pain threshold when compared to placebo. Remarkably, inhalation of cannabidiol increased plasma concentrations of THC, but decreased its analgesic effects, which could indicate synergistic pharmacokinetic interactions, but pharmacodynamic antagonism between THC and CBD. It should be noted that one of the limitations of this study was the short period of time in which it was carried out, as well as the number of patients included; additionally, although patients who indicated recent cannabis use were excluded, no exact time limit is stipulated to make this reservation. As an advantage, this study had a single route of administration (vaporization) [45].

Recently, Giorgi et al, in 2020 published an observational study, which includes 102 patients with fibromyalgia and VAS ≥ 4 despite standard analgesic treatment. The patients were prescribed two cannabis extracts diluted in oil: Bedrocan (22% THC, <1% CBD) and Bediol (6.3% THC, 8% CBD). The severity of fibromyalgia was assessed periodically using the Fibromyalgia Impact Questionnaire Revised (FIQR), the Fibromyalgia Assessment Scale (FAS), the FACIT-Fatigue score, the Pittsburgh Sleep Quality Index (PSQI), and the Zung Depression and Anxiety scale. The percentage of permanence in the study at 6 months was 64%. A significant improvement in PSQI and FIQR was observed in 44% and 33% of patients, respectively. 50% showed a moderate improvement in the anxiety and depression scales. Concomitant analgesic treatment was reduced or discontinued in 47% of the patients. One third of the patients experienced mild adverse events [46]. Among the strengths of this study is its adequate diagnosis of patients following the validated criteria for fibromyalgia, a relatively large number of patients who completed the study, the long period of treatment (6 months), knowledge of the composition of the cannabis supplied (ratio of THC and CBD) and the fact of handling a single route of administration (oral). The limitations of the study are mainly its observational design, which does not allow a comparison with a control group and the fact that the patients were treated with two preparations that have different THC / CBD ratios, which makes it difficult to differentiate between the two effects of each active ingredient [46].

In 2020 a critical review about the role of cannabinoids in fibromyalgia is published [47], including the most relevant studies between 2015 and 2019 [41-45]. It concludes that critically reviewed studies superficially suggest that medical cannabis is a safe product and an effective treatment for pain in fibromyalgia, however, serious methodological limitations prevent a definitive conclusion on the use of cannabinoids for the treatment of fibromyalgia pain in fibromyalgia patients [47].

Conclusions

The use of cannabinoids as part of the adjuvant management in fibromyalgia is promising in fact there are well-founded theories where it is considered that this pathology causes a deficiency in the endocannabinoid system, which would explain the adequate response to the use of exogenous cannabinoids [30,31].

The studies carried out to date would show effectiveness with minimal adverse effects, however, the multiple variables that can affect the results cannot be ignored [41,42,47], among other reasons for the faults in the design of the studies, the moderate to high risk of biases, the limited number of participants, the variability in the inclusion criteria, the non-standardization between the proportions of THC and CBD, the different routes of administration, the short duration of exposure to the cannabinoid, the different criteria for the diagnosis of fibromyalgia and the different existing strains of cannabis

The existence of a great variety of cannabis plants results in a wide range of biological and chemical characteristics in the products obtained from them, this means that not only THC and CBD have an important role in the physiological response after consumption, therefore, the role of other compounds such as flavonoids and terpenoids should not be underestimated, considering that there are a hundred of them with the possibility of contributing to the medicinal effect. The latter becomes another important limitation, since only some studies talk about the proportion of THC and CBD administered and none of them give importance to the other substances mentioned.

Having previously exposed the most relevant literature on the use of cannabinoids in fibromyalgia, it can be concluded that more research is needed to determine the clinical benefits not only in pain but also in the other symptoms that accompany this pathology, as well as more studies that cover the ideal composition of cannabis to establish the best possible therapeutics, the tolerability profiles of the different strains and compositions of cannabis, the ideal route of administration and the appropriate dose.

Recognitions

Contributions from the authors:

1. Author 1 (GWRJ). Study planning, literature review, interpretation of results, critical review of the manuscript.
2. Author 2 (KAOA). Concept of the original project, study planning, literature search, literature review, interpretation of results, initial writing of the manuscript.
3. Author 3 (JFGM). Study planning, literature search, literature review, final writing of the manuscript.

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- **Financial support and sponsorship:** none.
- **Conflicts of interest:** none.
- **Acknowledgment:** none.

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