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NARRATIVE REVIEW

Efficacy of cannabinoids in fibromyalgia: a literature review

Eficacia de los cannabinoides en la fibromialgia: revisión de la literatura

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Abstract

Fibromyalgia is a chronic disease of unclear etiology, involving a neural oversensitization and impaired pain modulation, in addition to a clinical deficiency of the endocannabinoid system. Fibromyalgia is associated with a number of somatic and psychological disorders and hence multiple pharmacological approaches have been used, including opioids, antidepressants, antiepileptics, and more recently medical cannabis. This narrative review comprises a review of the current literature on the efficacy of cannabinoids in fibromyalgia. The studies describe a possible influence of cannabis on pain control in patients with fibromyalgia, with positive effects on quality of life and sleep. The use of cannabis seems to be beneficial in patients with fibromyalgia; however, more robust studies are still needed to establish is actual efficacy in pain management, quality of life and improvement of associated symptoms.

Keywords

Fibromyalgia; Medical marijuana; Cannabinoids; Dronabinol; Tetrahydrocannabinol (THC); Cannabidiol (CBD).

Resumen

La fibromialgia es una enfermedad crónica, cuya etiología no es clara, en la que se involucra una sobresensibilización neural y disminución de la modulación del dolor, así como una deficiencia clínica del sistema endocannabinoide. Está asociada a una variedad de trastornos somáticos y psicológicos, por lo cual se han utilizado múltiples abordajes farmacológicos, entre ellos opioides, antidepresivos, antiepilépticos y, recientemente, cannabis medicinal. En esta revisión narrativa se hace una reseña de la literatura actual relacionada con la eficacia de los cannabinoides en la fibromialgia. Los estudios describen una posible influencia del cannabis sobre el control del dolor en pacientes con fibromialgia, con efectos positivos sobre la calidad de vida y el sueño. El uso del cannabis parece tener beneficios en los pacientes con fibromialgia; sin embargo, aún se requieren estudios más robustos para establecer su verdadera eficacia en el manejo del dolor, calidad de vida y mejoría de los síntomas asociados.

Palabras clave

Fibromialgia; Marihuana medicinal; Cannabinoides; Dronabinol; Tetrahidrocannabinol (THC); Cannabidiol (CBD).

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INTRODUCTION

Fibromyalgia is a chronic and complex disease, characterized by moderate to severe pain in specific musculoskeletal sensitive points, accompanied by sleep disorders, fatigue, headache, general malaise and even diseases such as irritable bowel syndrome, interstitial cystitis, and cognitive disorders. (1,2)

It was originally described by Gowers in 1904, with the term fibrositis, as generalized and diffuse pain affecting muscles and joints, due to an inflammatory component. However, it was not until 1950 that the true basis of the disease was questioned and in 1990 it was defined by the American College of Rheumatology as fibromyalgia. (3)

Fibromyalgia affects between 2-5 % of the population (4,5) and is more frequent in women with a mean age between 30 and 50 years. (6) Pain is the predominant symptom, accompanied by signs such as allodynia and hyperalgesia associated with an abnormal pain response. (4,7)

This becomes a challenging disease for medical services, since the current pharmacological interventions for chronic pain are not always useful. This results in patients being prescribed a lot of analgesic medications and interventions that are rarely successful. Pharmacological therapy includes antidepressants - noradrenaline reuptake inhibitors, anti-neuropathic drugs such as pregabalin, opioids and new pharmacological targets based on α2-δ ligands and cannabinoids such as nabilone. (8-10)

Notwithstanding the fact that the treatment of patients with fibromyalgia also includes other interventions, such as education and cognitive-behavioral (11), there rarely make a satisfactory impact on the life of patients.

The Food and Drug Administration (FDA) has not approved new drugs for fibromyalgia since 2009 (12,13). However, the search for new tools for managing these patients has been constant and the analgesic and immunomodulator effects of cannabis have come to light. (14) In the research on such effects, studies have shown that 77 % of the patients who received medical cannabis in Arizona reported experiencing almost complete pain relief and the reduction in the use of other medications, such as opiates. (15,16)

Due to similar findings in other studies, cannabis and its derivatives are being constantly investigated for the management of pain in fibromyalgia, its associated symptoms and quality of life. (17)

FIBROMYALGIA, THE CANNABINOID SYSTEM AND CANNABIS

The pathophysiology of fibromyalgia is based on the sensitization of the central nervous system affecting peripheral nociception and triggering chronic pain. Likewise, the imbalance in excitatory neurotransmitters, such glutamate and inhibitors such as serotonin and norepinephrine, and the endogenous opioid system, may be involved in pain perception, mood, and decreased energy, memory and sleep. (18)

Authors such as Russo and Smith have coined the term "clinical deficiency of the endocannabinoid system", in diseases such as migraine, irritable bowel syndrome, and fibromyalgia. This deficiency could be attributed to genetic or acquired reasons. (19,20)

The endocannabinoid system is present in all of us, and its main actors are anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (21), acting at the central and peripheral level via the cannabinoid receptors linked to proteins G: CB1R and CB2R and the proteins regulating their metabolism: monoacylglycerol lipase (MAGL) and fatty acid amidohydrolase (FAAH). (22)

However, the existence of various peptides and arachidonic acid derivatives that also interact with CB1R and elicit effects similar to the endocannabinoids, has also been described. Currently an "expanded endocannabinoid system" is being discussed, which includes these mediators belonging to the same chemical class as endogenous cannabinoids, not metabolically linked to AEA or 2-AG and which act on other proteins different from CB1R and CB2R. (23)

This system has effects on pain perception, mood, and sleep, inter alia (20) Cannabinoids act as neuromodulators of glutamate, gamma aminobutyric acid (GABA), serotonin, dopamine, norepinephrine and acetylcholine. Hence their spinal deficiency is associated with hyperalgesia and may become a target for optimal treatment.

There are three types of cannabinoids; the phytocannabinoids (in the cannabis plant) and the synthetic cannabinoids. These also bind to cannabinoid receptors and deliver a positive effect on pain perception. The primary psychoactive constituent is tetrahydrocannabinol (THC) which has shown analgesic effects, though it has been proven that there is a non-psychoactive constituent with anti-inflammatory, analgesic and anti-psychotic effects which is cannabidiol (CBD). (15,24)

These medicinal effects may be attributed to its influence on cannabinoid receptors, but also on the immune system. It has immunomodulatory effect over the immune cells such as B-cells, T-cells, monocytes and macrophages (25), with a reduction in the inflammatory response. (26)

THC acts as partial agonist of the CB1 receptors at the central level, inducing analgesia via the inhibition of the neurons activated by pain. CBD, in addition to its intrinsic analgesic and anti-inflammatory properties, binds to multiple pain-associated proteins, such as TRPV1, to desensitize them and achieve analgesia. Additionally, it improves the psychoactive effects of THC and others such as anxiety, sedation and tachycardia. (15)

The association between THC and CBD plays a key role in the pharmacological application of cannabis, since although THC is more potent in terms of its analgesic effects, it is also responsible for the psychoactive effects. CBD is less

potent but reduces the excitatory effects of THC in the CNS. For this reason, a pharmaceutical presentation needs a lower dose when based on THC and much more CBD to achieve similar effects. Hence, a balance between these two compounds is important in order to achieve a better effect of analgesia at with less potential adverse effects.

LITERATURE SURVEY

A systematic search was conducted in Medline: PubMed databases from February to May 2020, using the MeSH terms associated with the use of cannabis and its derivatives, in the treatment of pain in fibromyalgia. Clinical trials, review articles and original articles were included with no restrictions as to the year or language of publication. The terms used in the search were: Cannabis, Ganja, Hashish, Hemp, Bhang, Cannabinoids, Dronabinol, Tetrahydrocannabinol (THC), Marihuana, Cannabidiol (CBD), Cannabinol, Medical marijuana AND fibromyalgia.

Search strategy

Our search comprised a total of 110 references; the titles and abstracts of systematic reviews, meta-analyses, case reports, review articles and clinical trials were reviewed. The 50 most relevant were used to extract and organize data and for the drafting of the manuscript. The primary studies are shown in Table 1.

Primary studies

Clinical trials as a whole describe a likely influence of cannabis on pain in patients with fibromyalgia, with positive effects on quality of life and sleep. A clinical trial in 11 patients with fibromyalgia assessed a daily dose of δ-9-THC of 2.5 to 15 mg per day, increasing the dose by 2.5 mg each week. Of the 11 patients, 5 quit the trial because of side effects such as sedation, fatigue, and tiredness. However, the patients who completed the 3 months of treatment, experienced over 50% pain relief. (27)

Skrabet designed a randomized, double-blind, placebo controlled clinical trial with 40 participants receiving nabilone 0.5 and 1 mg twice a day, versus placebo. The patients described a significant reduction in the Visual Analogue Scale (VAS) for pain, as well as in the Fibromyalgia Impact Questionnaire (FIQR). (28,29)

In terms of sleep quality, Ware et al., conducted a controlled, randomized, crossover trial in 29 patients with fibromyalgia and insomnia. They received nabilone 0.5 mg or amitriptyline 10 mg. There was no difference in pain perception or quality of life among these patients, but there was a difference in terms of more restorative sleep. (30)

One of the studies with the largest number of patients was conducted by Sagy et al.: 367 people who received 670 mg of cannabis per day, followed by 1000 mg. 211 patients responded the follow-up questionnaire and reports a reduction in mean pain from 9 to 5 puntos (31). Another trial gathered a total of 383 patients using medical cannabis. Via an online questionnaire, 94% of the patients reported improved pain and 93 % reported improved quality of sleep; additionally, there was a low incidence of adverse effects (12 %). Nevertheless, the limitations of this trial should be kept in mind, because of the type of design and the way the information was collected. (32)

Fitz et al. assessed pain with VAS following a dose of cannabis: there was improvement of all symptoms and the perception of wellbeing was significantly higher. However, there were no differences in the Fibromyalgia Impact Questionnaire (FIQR) or in the Pittsburg Sleep Quality Index (PSQI). (55) Likewise, the studies by Yassin et al. and Giorgi et al., also showed a significant improvement in VAS, FIQR, PSQI ant the range of movement (ROM) of the joints. (33,34)

Secondary studies

A systematic review included 107 trials in patients with chronic pain, 7 on fibromyalgia. The randomized clinical trials showed superiority of cannabis for pain management in 30 % and a pain reduction with nabilone versus placebo in the same percentage. Tsang et al., in their systematic review found that, although it has a minimal effect on pain, it is significant and adverse events are marginal. (35) However, there was no impact on physical function or sleep improvement (36), (Table 2).

Walitt et al. and Lynch et al. conducted various systematic reviews of 20 controlled, randomized clinical trials, finding a significant effect of cannabis and its derivatives on pain and sleep. (37,38) Moreover, Fitz Charles et al., reported on four trials in which cannabinoids failed to show a significant contribution in the management of pain, but they did improve quality of life and anxiety in patients with fibromyalgia. (39,40)

DISCUSSION

The use of cannabis as a treatment for chronic pain, including neuropathic pain, as well as cancer and pain associated with rheumatic diseases such as fibromyalgia, has increased over the past decades . (41,42) The sustained use of medical cannabis has also been documented in these patients, at least over the first year of use, with minimal and tolerable adverse effects. (43) The studies have enabled the identification of its pharmacological characteristics and progress in society to reduce the stigmatization of its use. (41)

Studies in animal models have shown the effects of cannabinoids on pain, through their peripheral and spinal action. Different authors have assessed the role of cannabinoids on pain in Rhesus monkeys with specific molecules, such as WIN55,212-1, δ-9-TCH and AEA. (44-46) The results have shown that cannabinoids have an effect on pain modulation, although it

Table 1. Primary studies.

Author/yr	Type of study	Number of participants/doses	Results	Strengths	Weaknesses/biases
Fiz et al., 2011. (55)	Cross-sectional survey in patients with fibromyalgia recruited from a Rheumatology unit.	56 participants.	28 users of medical cannabis. The symptoms assessed with VAS [1] showed statistically significant improvement after 2 hours of self-administration of cannabis. The perception of wellbeing was significantly higher. No differences in the FIQR [2] were identified.	Clear inclusion and exclusion criteria. Information provided on use patterns by patients diagnosed with fibromyalgia.	The main bias is patient self-selection, in addition to the small sample size and variations in the use of cannabis among patients with fibromyalgia.
Schley, 2006. (27)	Clinical, controlled, prospective trial in patients with fibromyalgia in whim all medications had been removed.	11 participants. Daily oral dose of 2.5 to 15 mg, of δ-9-THC[3]. 2.5 mg increase each week.	7 of the 11 patients were excluded from the trial; 2 on their own decision, 5 because of side effects. Allodynia and hyperalgesia were not significantly affected by the medication. The medication with THC[3] significantly attenuated induced pain and pain perception. The patients who completed 3 months with THC[3], experienced over 50% pain relief, with a mean of 67 %.	Two approaches are suggested to monitor the different study variables, together with a clearly established dosage.	This is a pilot test so the sample size is small.
Ware, 2010. (30)	Clinical, controlled, randomized, crossover design trial in 2 phases.	29 participants. Nabilone 0.5 mg or amitriptyline 10 mg; the dose was doubled every week.	Nabilone had a stronger effect on sleep than amitriptyline in ISI[4]. A more restorative sleep was reported with the use of nabilone and easiness to fall asleep. No differences were found in terms of pain management and the perception of quality of life. The preference of the participants at the end of the trial was 41 % in favor of nabilone and 32 % for amitriptyline.	Amitriptyline and nabilone have similar side effects, with amitriptyline identified as a good control for nabilone, preserving the nature of the trial.	Due to the short duration of the exposure (two weeks) the results cannot be extrapolated to long-term management with nabilone.
Skrabek, 2008. (28)	Randomized, double blind, placebo controlled clinical trial in patients with fibromyalgia. 4-week follow-up.	40 participants. Nabilone 0.5 to 1 mg twice a day for 4 weeks versus placebo.	There was a significant decrease in VAS [1], the FIQR[2] and anxiety in the nabilone treated group at 4 weeks.	Shows the safety of short-term use of nabilone, paving the way to longer trials in this population.	Short duration of the trial, so the results may not be extrapolated to long-term management. In both groups the pain management the patient was receiving previously was not discontinued.

Author/yr	Type of study	Number of participants/doses	Results	Strengths	Weaknesses/biases
Habib, 2018. (32)	Retrospective cohort study of patients with a diagnosis of fibromyalgia and use of cannabis via an online questionnaire.	383 participants. 84 % use a mean dose of 31.4 +/- 16.3 mg.	94 % of the participants reported pain improvement and 93 % reported sleep quality improvement, Only 12 % reported adverse effects and about 92 % denied being addicted to cannabis.	Interesting description not just with regards to use habits, but in terms of social factors that may affected by cannabis use.	There may be sample biases due to patient self-selection. The time each patient has been using cannabis is also unclear, preventing any long term safety conclusions.
Sagy, 2019. (31)	6-month observational, prospective trial in a group of patients with fibromyalgia.	367 patients, with cannabis initial dose of 670 mg/ day, escalated to 1000 mg/day after 6 months (range between 700- 000 mg).	The pain intensity decreased from 9 to 5 (p <0,0001) in average; 81.1 % achieved treatment response. The most frequent adverse effects were dizziness (7.9 %), dry mouth (6.7 %) and GI symptoms (5.4 %).	Patients were followed for 6 months, long enough to observe the long-term effects of the medication.	Observational study that does not allow for establishing causality between the use of cannabis and decreased symptoms in fibromyalgia.
Habib, 2018. (56)	Retrospective study in patients with fibromyalgia managed with medical cannabis.	26 patients. Dose: 26 +/- 8.3 g per month and less than 1 g per day was enough to control the symptoms.	The mean treatment duration was 10.4 +/- 11.3 months, with a mean duration of 3 months. None of the patients discontinued therapy. All patients reported significant improvement in all the parameters of the survey. 13 patients stopped taking any other medications for fibromyalgia and 8 patients experienced very mild adverse effects.	Clear and accurate description in the methodology of all the clinical, demographic and laboratory variables.	Patients were included regardless of how long they had been using cannabis, which may result in biases in the reporting of both negative and positive effects.
Yassin, 2018. (33)	Observational crossover trial of one single center.	31 patients. 5 mg of oxycodone hydrochloride and 2.5 mg of naloxone twice a day and 30 mg of duloxetine once a day for 3 months. Subsequently 20 mg of inhaled medical cannabis (1:4 THC / CBD) for 6 months.	The initial medication was called SAT[5]. This led to an improvement versus the baseline. Therapy was initiated with medical cannabis and there was a significant improvement in all patients at 3 months and continued at 6 months. The informed results included improvements in FIQR[2], VAS[1], ODI[6] and ROM[7].	The inclusion criteria of the participants are clear, in addition to having a comprehensive and clear description of the study methodology. The crossover design reduces treatment variability with matched results.	Uses a small sample that prevents generalization of the results. The outcomes may not necessarily be due to the use of cannabis, since the initial SAT medication was concomitant in the patients. Moreover, patients knew that limited pain relief would give them access to cannabis therapy, resulting in a major bias that may be eliminated in future trials, including the comparison against placebo.

Author/yr	Type of study	Number of participants/doses	Results	Strengths	Weaknesses/biases
Giorgi el al., 2020. (34)	Observational, prospective study.	102 patients. Diluted extracts: 10-30 drops of bedrocan (22 % THC3 - <1 % CBD8) in the evening and 10-30 drops of bediol (6.3 % THC³, 8 % CBD8) in the morning.	A significant 44% improvement was observed in the PSQI9 and of 33 % in the FIQR2. 1/3 of the patients experienced mild adverse events. The need for other medications was reduced in 47 % of the patients.	Makes a detailed description of the study methodology and the presentations of the medical cannabis used, making it reproducible. Specifies that the treatment strategy is empirical and based on clinical experience.	The study was completed in only 66 of the original 102 patients. The design of the study does not allow for comparisons against a control group. Furthermore, the concomitant use of 2 presentations of medical cannabis prevents the differentiation of the effects of each presentation.
Ste Marie et al., 2012. (42)	Estudio observa-cional prospectivo.	457 patients referred for consultation: 302 patients with fibromyalgia. 47 patients used herbal based preparations 0.5 to 6 g/day. 13 patients used nabilone and 1 patient used dronabinol. The doses of the cannabinoids were established.	13 % of the patients referred to a pain center reported the use of cannabinoids with medicinal purposes. Smoked cannabis was the most popular. The opioid-seeking behavior and the current disease were associated with the use of herbal-based cannabis in the total cohort, but vanished when analyzed only in patients with fibromyalgia.	There are significant questions about the concomitant effects of cannabinoids and opioids. Makes a sound diagnosis of fibromyalgia in the participants.	The study is based only on the data provided by the pharmacy; therefore, only the medications dispensed are considered as used. The indications for use of cannabinoids are unclear and the diagnoses are obtained from administrative data only.
Alkabbani et al., 2019. (43)	Cohort study.	5452 new users of medical cannabis.	18.1 % of the patients used cannabinoids at one year. The mean use duration was 33 days for nabilone and 20 days for nabiximols. The longest use was found among patients between 19-45 and 46-64 years of age and with the highest socioeconomic level. Fibromyalgia was one of the diagnosis mostly associated with prolonged use (HR= 0,89 % IC=95 %).	Assesses the use of Sativex®, a pharmacological presentation available in Colombia. The description of the methodology enables the reproducibility of the trial in different settings or places.	The study is based only on the data provided by the pharmacy; therefore, only the medications dispensed are considered as used. The indications for use of cannabinoids are unclear and the diagnoses are obtained from administrative data only.

Author/yr	Type of study	Number of participants/doses	Results	Strengths	Weaknesses/biases
Habib, 2020. (57)	Observational, descriptive and prospective trial.	101 patients diagnosed with fibromyalgia and previously users of medical cannabis.	The mean duration of cannabis use was: 15.3 months and the monthly average amount used: 28.6 gr. 54 % smokes pure cannabis, 18 % vaporized and 3 patients used oil. 47 % of the patients discontinued other therapies and 51 % reduced the doses of other medications for fibromyalgia. The mean improvement in sleep and pain was 77 %. All patients recommended the treatment with medical cannabis to their loved ones. One fourth of the patients reported adverse effects and these were mild.	A broad characterization of the patients using medical cannabis at the personal, social, and other levels is provided. The results correspond to patients with a diagnosis of fibromyalgia, showing the benefits of medical cannabis versus the use of other pain medications.	No assessment of a specific presentation or dose of the medical cannabis is provided.
Van de donk, 2019. (50)	Experimental, randomized, placebo controlled trial.	20 patients. 4 varieties of cannabis: Bedrocan: 22.4 mg THC / >1 mg CBD. Bediol: 13.4 mg THC / 17,8 mg CBD. Bedrolite: <1 mg THC / 18,4 mg CBD. Placebo One inhalation.	The subjects receiving 13.4 mg THC and 17.6 mg CBD showed a 30% reduction in pain scores versus placebo. The variables with THC were associated with increased pain threshold.	Gives a very detailed description of the study methodology which makes it reproducible. Measures the plasma concentrations for improved correlation.	The sample size is too small, and the treatment period is too short; uses non-validated experimental measures. Does not provide direct evidence of the clinical use of cannabis.
Weber, 2009. (51)	Multicenter experimental study.	172 patients. 7.5 mg of δ-9-THC during 7 months.	48 patients discontinued the trial because of adverse events. 124 patients were assessed via a multicentric survey. The parameters: PDI[10], QLIP[11], HADS[12] and pain intensity improved significantly. There was a reduction in the use of opioids.	The methodology described allows for reproducing the trial in the future. Established the doses used of δ9-TCH.	One single telephone survey was administered, with no follow-up. There were several interviewers assessing the parameters, therefore there may be variations in the results. The selection criteria are very few, hence the group of patients is very heterogeneous and the results may not be addressed to specific situations.

[1] Visual Analogue Scale. [2] Fibromyalgia Impact Questionnaire. [3] Tetrahydrocannabidol. [4] International Sensitivity Index. [5] Standarized Analgesic Therapy. [6] Oswestry Disability Index. [7] Range of Movement. [8] Cannabidol. [9] Pittsburgh Sleep Quality Index. [10] Pain Disability Score. [11] Pain Related Quality of Life Impairment. [12] Hospital Anxiety and Depression Scale.

Source. Authors.

Table 2. Secondary Studies.

Author/yr	Type of review	Population	Studies included	Intervention	Results	Strengths	Weaknesses / biases
Stocking, 2018. (36)	Systematic review and meta-analysis of controlled and observational trials.	Patients with non-cancer chronic pain, fibromyalgia and rheumatoid arthritis.	104 trials were included, of which 7 were on fibromyalgia.	Cannabinoids.	The randomized clinical trials showed 30 % superiority of cannabis for pain. The observational trials found that nabilone reduced pain by 30 %. There was no significant impact on physical and emotional function and in sleep improvement.	Has the limitations of most of the trials associated with cannabis and cannabinoids in non-cancer chronic pain conditions: includes each of the clinical entities, as well as the various presentations and routes of administration of these medications. Describes the findings (domains) considering pain, functionality, adverse events, satisfaction and emotions in the population studied.	Includes trials of diverse statistical value and methodological design. The results are for chronic, non-cancer pathology in general; no specific statistical analysis for fibromyalgia. The observational studies included have a high risk of bias in the domains assessed..
Fitzcharles, 2016. (39)	Systematic review of randomized controlled trials.	Patients with chronic pain associated with rheumatic diseases: fibromyalgia, back pain, osteoarthritis and rheumatoid arthritis.	4 studies were included, of which 2 were on fibromyalgia.	Nabilone 0.5-1 mg	Cannabinoids did not show superiority versus placebo; no report on 50% pain reduction. No significant difference between fatigue and depression, but there was a significant difference with anxiety and quality of life. There were no severe adverse events.	Includes controlled, double blind clinical trials. The studies assessed on the use of cannabinoids in fibromyalgia include the same intervention.	The sample assessed in patients with fibromyalgia in enough for a direct analysis of the use of medical cannabis in fibromyalgia.
Walitt, 2016. (37)	Systematic review of randomized controlled trials.	Patients with fibromyalgia.	2 studies with 72 patients with fibromyalgia were included.	Nabilone 1 mg / day.	The patients reported pain relief, without a qualitative analysis of this variable. There were no significant differences in terms of anxiety and depression, but nabilone did show superiority over amitriptyline with regards to sleep. None of the trials reported severe adverse events.	The studies assessed on the use of cannabis include the same intervention.	These are very limited studies to make a final conclusion. The results are classified as very low quality evidence with probable report biases .

Author/yr	Type of review	Population	Studies included	Intervention	Results	Strengths	Weaknesses / biases
Lynch, 2011. (38)	Systematic review of randomized trials.	Patients with chronic non-cancer pain: dolor neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	18 trials were included.	Smoked Cannabis, cannabis-based oral-muscle-nasal extracts, nabilone, dronabinol and THC analogue.	15 of the 18 studies showed a significant effect of cannabinoids on pain, versus placebo. Improved sleep was reported in patients, Adverse events were well tolerated.	The studies included are an initial approach to medical cannabis and its potential effect on chronic pain modulation.	The studies included are of small sample size and short duration, therefore it is impossible to discuss efficacy and safety of medical cannabis. Only one study on cannabinoids and fibromyalgia is included.
Mucke, 2018. (52)	Review of controlled, double blind, randomized trials.	Patients with chronic neuropathic pain.	16 studies were included.	Comparison: oral mucosa spray of THC/ CBD, nabilone, cannabis inhaled herbal product, dronabinol and dihydrocodeine.	The use of cannabis may achieve a 50% pain improvement or more, as compared to placebo. The adverse events were more severe in patients with cannabis versus placebo.	Includes a large number of patients assessed with neuropathic. All cannabis-based medications showed better results in reducing pain intensity, sleep disorders and anxiety as compared to placebo.	The use of different cannabis-based medications results in different outcomes with regards to the effect on neuropathic pain. In general, the studies analyzed are short in terms of their implementation, There no evidence of high quality. No results on the Inappropriate use or potential abuse of cannabis-based medications.
Tsang C, 2016. (35)	Systematic review of controlled, randomized trials and prospective cohort studies.	Patients with chronic neuropathic pain: cancer, non-cancer, fibromyalgia and spasticity.	11 studies were included.	Nabilone.	Nabilone resulted in minimal but significant pain reduction in patients with chronic neuropathic pain. Adverse reactions included euphoria, somnolence, and dizziness.	The studies analyzed include the same intervention with nabilone. Collection and summary of data on efficacy and safety of the use of nabilone in chronic pain syndromes.	The studies analyzed have a small sample size, and short duration. The dose-effect relationship for nabilone could not be established.

Source. Authors.

may be dose-dependent. Moreover, Fox et al., Hsieh et al., and Bridges et al., assessed the cannabinoids and their effect on hyperalgesia, hyperalgesia, allodynia and neuropathic pain in mice. (45,47,48) Bridges assessed WIN55,212-2, the thresholds of hind limb withdrawal thresholds to cold, mechanical and noxious thermal stimuli. (48) The data showed the therapeutic potential of cannabinoids in neuropathic pain caused by the CB1R receptor. (47,48)

While the preclinical trials did not focus on specific diseases such as fibromyalgia, they do focus on a set of symptoms and signs present in chronic pain diseases. This means that cannabis may become a new focal point for research in this condition.

THC and CBD interact with the endocannabinoid system to reduce and manage pain, which results in improved quality of life for patients with chronic neuropathic pain. (49) It is important to highlight a preference for the use of CBD, since THC is responsible for the psychoactive effects in the central nervous system and has been associated with more adverse effects.

In their most recent study, Habib et al., assessed 101 patients with a diagnosis of fibromyalgia who had already started

using cannabis with medicinal purposes. In addition to the positive effects on pain and sleep, they found a very positive response to treatment; 47 % discontinued the use of other drugs and 51 % reduced the doses of other medications. The mean pain improvement in pain and sleep was 77 %, and only one fourth of the sample experienced mild adverse events. All patients recommended the therapeutic use of cannabis (32). The dose reduction of other medications was also shown in the study by Weber et al. (51)

Van de Donk et al. conducted a randomized trial with four arms in 20 patients with fibromyalgia. They tested three varieties of medical cannabis with different amounts of THC and CBD vs. placebo, administered inhaled. They assessed the thresholds for electrical and pressure pain, the spontaneous pain scores, and the blood levels of the drug for three hours. While cannabis did not show any effect on spontaneous or electrical pain, it did show effects on pressure pain as compared to placebo ($p < 0.01$). Moreover, the subjects receiving higher THC doses showed a 30% reduction in pain scores as compared to placebo ($p < 0.01$). However, they emphasize the need to conduct further studies to determine the long-term treatment effects on pain scores, the CBD-THC interactions, and their associated analgesic response. (50)

The adverse effects findings are heterogeneous; some trials report low prevalence while report rates of up to 25% of adverse effects and/or dropout rates. (51) Schley et al., had 7 of 11 patients that quit the trial because of intolerable nausea, vomiting and dizziness. (27)

A big controversy arising from these trials relates to which is really the appropriate dose, how should it be administered and whether the potential beneficial effects outweigh the risks and/or harm. (50,52) There are studies that establish a dose of 15 mg of THC equivalent and progressively increase the dose based on tolerance. (53) However, these doses are variable in the different studies considered, and additionally the concentrations of THC/CBD in their presentations are not specified, neither the mode of administration.

In Colombia, the use of cannabis with medical purposes was regulated in 2016 with Law 1787. However, not much progress has been observed in terms of cultivation processes, production and manufacturing of cannabis byproducts for use in chronic diseases. Moreover, the scope for its use under the healthcare social security system has not been defined. (54) Currently in our country, Sativex® is the only product approved to be marketed for clinical use. (54) Similarly, compounding preparations are a pharmacological option for prescription in our country, prior approval by the INVIMA (The Colombian National Institute of Drug and Food Oversight) . However, no studies were found reflecting the evidence of these preparations, and therefore there are limitations to extrapolate their results.

This review provides the outlook on cannabis and its use in fibromyalgia; it acknowledges the lack of available literature and the difficulty this represents to generalize both the positive and negative effects of medical cannabis for pain management, insomnia, anxiety and mood disorders in these patients. An additional limitation is that the different articles fail to include clear inclusion and exclusion criteria, which hinders the characterization of the samples assessed. This review tried to include most of the literature on the topic; however, there may be some limitations in the selection and appraisal of the evidence found.

With the current state of the literature, it is difficult to make strong recommendations about the use of cannabis-based medicines for the management of patients with fibromyalgia. Further clinical trials and observation studies are needed to clearly establish the potential risks and benefits.

The available literature on cannabis and its effects on diseases with prevalent pain, has not been able to establish a level of effectiveness to recommend its use. It should be highlighted that there is limited availability of scientific studies with the best clinical evidence. Therefore, there is a need to conduct more comprehensive studies and clinical trials to establish its actual efficacy in terms of pain management, quality of life, and improvement of associated symptoms, as well as the impact on the use of other medications for managing chronic pain. Moreover, it is important to acknowledge the different methods that can be used to administer cannabis, and based on that, to identify any variations in dosing and optimal amounts of tetrahydrocannabinol and cannabidiol for patients.

ETHICAL DISCLOSURES

This paper was considered free of risk according to Resolution 8340 of 1993 of the Ministry of Health, establishing the scientific, technical, and administrative standards for health research.

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Contributions by the authors

HJMA: Inception, design, planning of the study, data analysis, preliminary and final draft of the manuscript and final approval.
OFGR: Inception, design, planning of the study, data collection, data analysis, interpretation of the results, preliminary draft and approval of the final manuscript.
MPTO and DHFV: Data collection, data analysis, interpretation of the results, preliminary and final draft of the manuscript, and final approval of the manuscript.

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