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Medicinal Cannabis for Patients with Fibromyalgia: A Review

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Abstract: *Cannabis sativa* is a plant that has been used for millennia in the treatment of conditions such as chronic pain, rheumatism and epilepsy. Biochemical and molecular studies have isolated its components, which are known as cannabinoids, and have mapped a complex system of endogenous molecules and receptors, known as the endocannabinoid system. Studies report the importance of this system in the physiopathology of different organic disorders, such as fibromyalgia, Parkinson's disease and neoplasms. Advances in Brazilian legislation have enabled the investigation and use of cannabis oil in the treatment of illnesses and there is growing interest in the potential of medicinal cannabis for the treatment of conditions associated with chronic pain, such as fibromyalgia. Studies have been developed on the safety and effectiveness of cannabinoids for the treatment of patients with fibromyalgia. However, long-term prospective clinical studies involving patients with fibromyalgia treated with medicinal cannabis oil are needed, with a focus on aspects related to pain, anxiety, depression and quality of life.

Keywords: *Cannabis sativa*, Endocannabinoid System, Chronic Pain, Fibromyalgia

Introduction

The history of *Cannabis sativa* goes back millennia and is linked to the history of human evolution itself. Studies report the use of the plant for at least 5000 years.[1] Historical documents demonstrate that *Cannabis* was used as a medicine in China at least 2700 years BCE for different conditions, such as rheumatism, intestinal constipation and malaria.[2]

In 1974, Israeli researcher Raphael Mechoulam published an important study on the isolation of the components of cannabis, known as phytocannabinoids.[3] The researcher identified more than 120 cannabinoid substances, the best known of which are Δ9-tetrahydrocannabinol (TCH) and cannabidiol (CBD), contributing to the broad dissemination of studies on the active components of the plant.[4]

The use of medicinal cannabis has recently become popular following approval in the United States, Canada and European countries, such as Germany, Sweden, Norway, Switzerland and Portugal.[5,6] In Brazil, the National Agency of Health Surveillance promoted a set of measures in recent years, such as the approval of the importation of medications with components of *Cannabis sativa*.[7]

Such legislative advances enabled an increase in scientific production in search of evidence on the effectiveness of cannabis-based medication for diverse clinical conditions. A systematic review with meta-analysis conducted by Canadian researchers analyzed 32 randomized clinical trials totaling 5174 patients with chronic oncological and non-oncological pain, reporting mild improvements in pain intensity, quality of life and sleep quality.[8] Thus, medicinal cannabis is promising for the treatment of chronic pain and should be studied further.

Endocannabinoid System

Studies in the 1990s discovered cannabinoid receptors and endogenous cannabinoids, which became known as the endocannabinoid system. Such molecular studies reported the presence of two types of receptors (CB-1 and CB-2) capable of bonding to compounds of *Cannabis sativa*, especially THC.[9] Besides these receptors, endogenous lipids were identified that serve as neurotransmitters and have a similar chemical structure to that of phytocannabinoids, interacting with the CB-1 and CB-2 receptors.[10] These lipids became known as endogenous cannabinoids. The main endogenous cannabinoids are anandamide and 2-arachidonoylglycerol (2-AG).[11,12]

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Various molecular studies and quantification methods of endogenous cannabinoids and cannabinoid receptors have demonstrated changes in this system in metabolic disorders, such as Parkinson's disease,[13] cirrhosis[14] and cancer.[15,16] The study of the endocannabinoid system demonstrates immense potential for the exploration of disorders as well as the therapeutic potential of cannabinoids.[17]

Fibromyalgia

Fibromyalgia is one of the main causes of chronic pain and is characterized as a complex disorder involving diffuse musculoskeletal pain, fatigue and sleep disorders.[18] The prevalence of fibromyalgia in the world population ranges from 2 to 8% and the condition is more common in women.[19] This disease has a considerable negative impact on quality of life not only in terms of physical aspects, but also psychological aspects and is commonly associated with depression, anxiety and other psychiatric disorders.[20]

The etiology of fibromyalgia is uncertain. The disease has a multifactorial nature that encompasses genetic predisposition, disorders in the regulation of neurotransmitters related to pain sensitivity, inflammatory disorders and triggers related to the environment, such as stress, trauma and infections.[19]

The diagnosis of the fibromyalgia is performed using the criteria of the American College of Rheumatology published in 2010 (ACR – 2010), which consider the following aspects: (1) symptom severity scale and widespread pain index; (2) the presence of symptoms for at least three months; and (3) the absence of another disorder that may explain the pain.[21]

Treatment is multidisciplinary and includes both pharmacological and non-pharmacological measures. The therapeutic arsenal includes antidepressants, anticonvulsants, muscle relaxers and analgesics. Non-pharmacological measures include psychotherapy, physical exercise and psychoeducation.[22]

Despite the therapeutic possibilities, there is no cure for the disease, which leads many individuals to adopt measures with a greater risk of adverse events, such as the use of opioids. Patients with fibromyalgia have a greater likelihood of being prescribed opioids, which increases the odds of abuse, dependence and overdose.[23,24] Thus, it is of extreme importance to encourage studies that seek novel therapies capable of reducing pain levels and improving quality of life in individuals with fibromyalgia.

Fibromyalgia and Medicinal Cannabis

There is growing interest in the potential of medicinal cannabis for the treatment of conditions associated with chronic pain, such as fibromyalgia. Studies have been developed on the safety and effectiveness of cannabinoid-based treatment.

A prospective study involving 367 patients with fibromyalgia taking cannabis oil [average of 140 mg/day (range: 90 to 200 mg) of THC and 39 mg/day (range: 10 to 69 mg) of CBD] for at least six months demonstrated a significant improvement in pain levels, confirming the safety and effectiveness of this therapeutic modality.[25] Further studies are needed to assess the efficacy of treatment.

In a study conducted in Italy, 66 patients with fibromyalgia who had no response to conventional treatment were treated with cannabis-based medications for six months, continuing or not with concomitant analgesic treatment.[26] Improvements were found in sleep quality (44%) and anxiety and depression (50%) and approximately one-third exhibited only mild adverse events.

Studies have also investigated the possibility of a direct link between fibromyalgia and dysfunctions of the endocannabinoid system. A study comparing the serum concentration of anandamide in patients with fibromyalgia and a control group found a significant increase in this compound in the fibromyalgia group, indicating an increase in the peripheral activity of the endocannabinoid system.[27]

A review suggested that the state of hyperalgesia found in some patients may occur due to the dysfunction of the endocannabinoid system, altering nociceptive regulation.[28] Support to this theory is found in preclinical studies involving rats, which demonstrated that the intrathecal injection of SR141716A – a potent antagonist of endocannabinoids – promoted a state of hyperalgesia.[29]

Conclusions

Medicinal cannabis as part of the therapeutic arsenal opens a broad horizon of possibilities in medical practice. Patients who suffer from chronic pain caused by fibromyalgia have increasingly benefited from this therapy. However, studies are scarce and there is a need for more research in this field.

Fibromyalgia is complex disease with an uncertain etiology. Recent studies report the possible involvement of dysfunction of the endocannabinoid system in the physiopathology of the disease. Evidence points to a significant reduction in pain and improvement in quality of life in patients who use cannabis oil. Clinical trials and prospective studies are needed to determine the effectiveness of treatment.

The disease is characterized not only by physical pain, but also compromised quality of life, with

symptoms and associated comorbidities, such as depression, anxiety and insomnia. Thus, validating therapies that propose a multisystemic approach rather than focused only on pain relief could assist a large portion of society that suffers the negative impacts of fibromyalgia.

The studies discussed in this paper demonstrate the safety of the drug and report minimal side effects, such as dry mouth, nausea/vomiting and hyperactivity.[27] Moreover, there is a greater risk of the abuse of opioids on the part of individuals refractory to conventional therapy for fibromyalgia. Thus, it is important to validate cannabis oil, since the medication has not demonstrated the risk of dependence, as occurs with opioids.

With the judicial determinations of the National Health Vigilance Agency (ANVISA) and the recent approval of the use of cannabis oil via the public healthcare system in the state of São Paulo, Brasil[30], there is need for further clinical studies to serve as the basis for physicians to prescribe the new medication. There is also a need for long-term prospective clinical studies involving patients with fibromyalgia treated with medicinal cannabis, emphasizing aspects related to pain, anxiety, depression and quality of life.

Conflict of Interests

The authors have no conflict of interests to declare.

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