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Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia

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Fibromyalgia is a complex disease process that is as prevalent as it is poorly understood. Research into the pathophysiology is ongoing, and findings will likely assist in identifying new therapeutic options to augment those in existence today that are still insufficient for the care of a large population of patients. Recent evidence describes the use of cannabinoids in the treatment of fibromyalgia. This study provides a systematic, thorough review of

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the evidence alongside a review of the seminal data regarding the pathophysiology, diagnosis, and current treatment options. Fibromyalgia is characterized by widespread chronic pain, fatigue, and depressive episodes without an organic diagnosis, which may be prevalent in up to 10% of the population and carries a significant cost in healthcare utilization, morbidity, a reduced quality of life, and productivity. It is frequently associated with psychiatric comorbidities. The diagnosis is clinical and usually prolonged, and diagnostic criteria continue to evolve. Some therapies have been previously described, including neuropathic medications, milnacipran, and antidepressants. Despite some level of efficacy, only physical exercise has strong evidence to support it. Cannabis has been used historically to treat different pain conditions since ancient times. Recent advances allowed for the isolation of the active substances in cannabis and the production of cannabinoid products that are nearly devoid of psychoactive influence and provide pain relief and alleviation of other symptoms. Many of these, as well as cannabis itself, are approved for use in chronic pain conditions. Evidence supporting cannabis in chronic pain conditions is plentiful; however, in fibromyalgia, they are mostly limited. Only a handful of randomized trials exists, and their objectivity has been questioned. However, many retrospective trials and patient surveys suggest the significant alleviation of pain, improvement in sleep, and abatement of associated symptoms. Evidence supporting the use of cannabis in chronic pain and specifically in fibromyalgia is being gathered as the use of cannabis increases with current global trends. While the current evidence is still limited, emerging data do suggest a positive effect of cannabis in fibromyalgia. Cannabis use is not without risks, including psychiatric, cognitive, and developmental as well as the risks of addiction. As such, clinical judgment is warranted to weigh these risks and prescribe to patients who are more likely to benefit from this treatment. Further research is required to define appropriate patient selection and treatment regimens.

Introduction

Fibromyalgia is an illness characterized by chronic widespread pain (CWP) and a myriad of symptoms, including fatigue, sleep disturbances, cognitive dysfunction, and depressive episodes [1]. As a functional disorder, a diagnosis of fibromyalgia requires that the symptoms are not due to an underlying organic illness. There are no laboratory tests for fibromyalgia, and as a result, the diagnosis historically has been made clinically and is based on classification criteria designed by the American College of Rheumatology (ACR) in 1990 [2]. Based on advances in our understanding of this disease, new classification criteria were proposed and accepted in 2010 to include the associated psychosomatic symptoms beyond CWP. These criteria continue to evolve [3].

The definitive treatment of fibromyalgia is elusive. The process of diagnosis and effective treatment is laborious and complex and takes an average of two years until a diagnosis is reached [4]. The recent 2016 European League Against Rheumatism (EULAR) guidelines recommend that treatment should accomplish gains in the relief of pain, fatigue, sleep, and daily functioning. Given the dearth of ideal treatment options, with physical exercise being the only treatment rated as strongly proven for fibromyalgia, recent efforts have been made to elucidate more therapeutic options for patients [5].

Cannabis is an ancient substance that has been used throughout antiquity to treat a variety of painful ailments [6]. Recent evidence suggests that cannabis could be an effective therapy for fibromyalgia. Cannabis interacts with the central nervous system (CNS) through endocannabinoid receptors and signaling molecules and produces analgesic and psychoactive effects. Cannabis' well-known psychoactive substance is known as tetrahydro cannabidiol (THC) or Δ9-Tetrahydrocannabinol. THC acts as an agonist of the endocannabinoid receptors resulting in reduced neurotransmission. Cannabis and its derivatives are divided into naturally occurring phytocannabinoids, such as cannabidiol (CBD) and synthetic cannabinoids, currently marketed as dronabinol. Of note, CBD lacks the THC-induced intoxicating properties known colloquially as "being high" [7]. Despite its legal history and prohibition in various countries, cannabis and CBD are currently available in most states of the USA as well as other countries around the world. Most states allow its use for Alzheimer disease, amyotrophic lateral sclerosis (ALS), cachexia/wasting syndrome, cancer, Crohn's disease, epilepsy and seizures, glaucoma, hepatitis C infection, AIDS, multiple sclerosis (MS) with muscle spasticity, severe and chronic pain, severe nausea, and post-traumatic stress disorder (PTSD) [8].

Here, we review the background, pathogenesis, and current treatment options for fibromyalgia. We proceed to review the evidence that exists to support or refute the usage of cannabis and cannabinoids in the treatment of fibromyalgia, the likely mechanisms, and comment on the side effects and appropriate patient selection for this treatment.

Fibromyalgia

Fibromyalgia is a multisymptom disorder, which is most often described as a disease of chronic pain. Historically, the diagnosis was made clinically in patients complaining of chronic widespread pain (CWP) with focal bilateral muscular tender points found on examination. Fibromyalgia frequently manifests with associated symptoms, including fatigue, sleep disturbances, cognitive dysfunction, and other comorbidities [9].

CWP and fibromyalgia are both disorders of pain regulation with central sensitization. A recent review suggested that the worldwide estimate of generalized chronic pain ranges from 10.6% to 11.8% [10]. Although the pathogenesis of both these syndromes is unclear, several mechanisms, including hyperexcitability of the central and peripheral nervous systems, pain receptor function, and somatization, have been hypothesized [11].

Epidemiology

Fibromyalgia is described as a disease of CWP, and epidemiological evidence suggests that CWP affects 10% of the population in several countries [12]. According to the 2016 Global Burden of Disease Study, pain and pain-related diseases are the leading cause of disability and disease burden globally [13]. In a survey of 4197 patients, it was found that patients with CWP had a poorer quality of life [14]. In a subsequent observational study, a survey found that patients with fibromyalgia have a poorer quality of life than patients with CWP alone [15]. A 2007 analysis of US health insurance providers determined that patients with fibromyalgia have high levels of comorbidities and high levels of healthcare utilization and cost [16].

Our current understanding of the epidemiology of fibromyalgia is limited to studies taking place in clinical settings and few have taken into account symptomatic persons in the general population [17]. Several large community-based studies have attempted to establish the prevalence of fibromyalgia [18]. Early estimates on regional prevalence range from 0.7% in Denmark in 1993 [19] to 2.4% in Spain in 2000 [20]. A 1995 population-based study in Wichita, Kansas, found that 2.0% of a sample of 3006 persons had fibromyalgia [21]. A 2005 population-based study in Minnesota found that 5.3% of the population of Olmsted County, Minnesota, were diagnosed with fibromyalgia [22]. A 2017 meta-analysis concluded that 1.78% of the general population globally suffers from fibromyalgia, and the prevalence of fibromyalgia is more common in women than in men [23]. The majority of epidemiology studies were conducted before the ACR redefined the diagnostic criteria in 2010, so an exact accounting of prevalence is elusive [24]. Despite the differences between these community-based studies, there is

also no evidence that the prevalence of fibromyalgia significantly differs regionally or socioeconomically [18].

Diagnostic criteria

The classification criteria of fibromyalgia were first published in 1990 by the ACR [21], with a sensitivity of 88.4% and specificity of 81.1% for the clinical diagnosis of fibromyalgia. They defined a positive diagnosis as the presence of 11 out of 18 specific focal tender points palpated during a physical exam. However, because focal tender points can be found in patients with no evidence of chronic pain, the assessment of focal points alone may not properly identify fibromyalgia in patients. In addition, associated symptoms such as fatigue, sleep disturbance, and cognitive dysfunction are also prominent. For these reasons, the original criteria were updated in 2010 to address comorbidities and associated symptoms. The criteria were further revised in 2016, to describe in detail about widespread chronic pain in terms of generalized pain demonstrated in 4 out of 5 regions [3]. The current definition of fibromyalgia incorporates both physical exam findings congruous with the ACR diagnostic criteria and pertinent patient history. Most recently, the American Pain Society has devised core diagnostic criteria incorporating three key parts; 1) musculoskeletal pain found in 6 of 9 body regions found in conjunction, 2) moderate to severe sleep problems or fatigue, and 3) symptoms lasting at least three months [3].

Comorbid conditions

Fibromyalgia is heavily influenced by psychosocial factors, with an abundance of psychiatric comorbidity occurring at rates as high as 30%–60% [1]. Furthermore, a 2006 prospective study found a substantial lifetime psychiatric comorbidity in individuals with fibromyalgia [25]. A multicenter study found a higher prevalence of major depression, anxiety disorder, and panic disorder as well as other psychiatric disorders among tertiary care fibromyalgia patients from across the USA [26]. Additionally, comorbidity between PTSD and fibromyalgia has been established because of commonality between symptoms and antecedent traumatic experiences in both disorders [27]. Sleep disturbance is a cardinal symptom of fibromyalgia, with only 30% of fibromyalgia patients reporting “optimal sleep” in a large cross-sectional study of 3035 fibromyalgia patients [28]. The association between fibromyalgia and rheumatological diseases (e.g., rheumatoid arthritis (RA), systemic lupus erythematosus, ankylosing spondylitis, osteoarthritis, etc.) has also been well established [29–32].

Pathophysiology

A number of factors have been attributed to the development of fibromyalgia, including abnormalities in the neuroendocrine and autonomic nervous systems, genetic factors, psychosocial variables, and environmental stressors [33]. Patients with fibromyalgia display enhanced sensitivity to stimuli, such as heat and cold as well as to mechanical pressure. These stimuli provoke pain response that would not otherwise be elicited in otherwise healthy individuals. Biochemical and neuroimaging data suggest that serotonergic and noradrenergic activities are attenuated in patients with fibromyalgia [34]. Patients with fibromyalgia were found to have reduced serum levels of serotonin and its precursor 1-tryptophan in addition to reduced CSF levels of the principal serotonin metabolite 5-hydroxyindoleacetic acid [35]. With these findings in mind, numerous pharmacotherapies with serotonergic and noradrenergic effects have been shown to exhibit some efficacy [1].

Considering the widespread nature of pain in fibromyalgia, alongside the most frequent CNS-mediated symptoms, i.e., fatigue, memory difficulties, sleep, and mood disorders, it has been postulated that the CNS amplifies the pain through neurotransmitter-mediated sensory transmission [36]. A feature known as diffuse noxious inhibitory control (DNIC) has been identified as a mechanism of pain inhibition that is consistently attenuated in fibromyalgia patients [37]. Normally through the DNIC, one pain normally inhibits another, but it is dysfunctional in fibromyalgia patients [38,39].

Through the use of functional magnetic resonance imaging, imaging studies have confirmed altered central neural processing in nociceptive pathways among fibromyalgia patients [40]. Also, involved in

the CNS excitation are neurotransmitters, such as substance P and glutamate. Substance P has been found to be elevated in the CSF of fibromyalgia patients [41], and in addition to substance P, glutamate has also been found to be elevated in both the CSF and the insula of the brain of fibromyalgia patients [42]. However, despite these findings, the exact pathogenesis of fibromyalgia has not been completely elucidated [43].

Current treatment modalities

In terms of treatment, clinical evidence suggests a multifaceted program emphasizing education, medication, exercise, and cognitive-behavioral therapy (CBT) [44]. In the USA, the FDA has approved the use of pregabalin, duloxetine, and milnacipran as monotherapy in the treatment of fibromyalgia. It is generally accepted that one of these monotherapies used in conjunction with nonpharmacological therapies yields the best results [9]. Pharmacotherapies with the strongest evidence (level 1A) for efficacy include: tricyclics (amitriptyline and cyclobenzaprine), dual reuptake inhibitors (venlafaxine, duloxetine, and milnacipran), and α_2 -δ ligands (pregabalin and gabapentin) [1]. Current EULAR guidelines report that nonpharmacological interventions, including aerobic exercise and strength training, are given the strongest recommendation for treatment [5].

Amitriptyline and cyclobenzaprine are tricyclic antidepressants (TCA) that increase the concentration of serotonin and/or norepinephrine by inhibiting their reuptake [1]. According to a meta-analysis, patients taking low-dose amitriptyline improved pain, sleep, and fatigue symptoms with low rates of discontinuation [5]. Cyclobenzaprine has more limited evidence with improvement shown mostly in sleep quality but not in fatigue. Side effects can manifest due to adrenergic, cholinergic, and histaminergic antagonism affecting the drugs' tolerability [45].

Dual serotonin and norepinephrine reuptake inhibitors (SNRI) are pharmacologically similar to TCAs as they also increase the concentration of serotonin and norepinephrine. However, their activity is more selective, limiting their effect on other receptors. As a result, SNRIs have fewer side effects and more tolerability when compared with TCAs [1]. In a randomized controlled trial (RCT), venlafaxine was found to be ineffective at low doses of 75 mg/dL but was found to be more effective at higher doses [46]. Milnacipran has been found to have more noradrenergic effects than duloxetine and is potentially more helpful for fatigue and memory problems but with greater risk for hypertension [9]. Duloxetine was found to be effective in women for the treatment of fibromyalgia with and without major depressive disorder in a double-blind, randomized clinical trial [47].

Pregabalin and gabapentin are both α_2 -δ calcium channel ligands. Pregabalin has been shown to improve neuropathic pain, sleep disturbances, and fatigue versus placebo in fibromyalgia patients [48]. Gabapentin is well used in neuropathic patients, and has been shown to be effective in fibromyalgia patients [49].

Other drugs with moderate evidence for efficacy include tramadol, selective serotonin reuptake inhibitors (SSRI), dopamine agonists, and γ-Hydroxybutyrate (GHB). SSRIs include fluoxetine, sertraline, paroxetine, and citalopram function by inhibiting serotonin reuptake and evidence for their efficacy has been inconclusive. Citalopram, a newer SSRI formulation, has greater selectivity for serotonin and was shown to be less effective in the relief of fibromyalgia symptoms as a result [45].

Tramadol is an analgesic compound with some opioid and serotonin/norepinephrine reuptake inhibition. It has been found to be moderately effective either as a monotherapy or when combined with acetaminophen [50]. GHB, also known as sodium oxybate, is a metabolite of γ-aminobutyric acid with sedative properties that has been shown to be efficacious in the relief of fibromyalgia, but is not yet approved by the FDA because of safety concerns [51].

Many drugs have shown not to be effective, including opioids, NSAIDs, corticosteroids, benzodiazepine, melatonin, guaifenesin, and dehydroepiandrosterone [44]. A recent Cochrane review examined combination therapies, including a nonsteroidal anti-inflammatory drug (NSAID) with benzodiazepine; combined therapy with amitriptyline and fluoxetine; melatonin combined with an antidepressant; paracetamol and caffeine; tramadol and paracetamol; and pregabalin with duloxetine. This Cochrane review found little evidence to support or refute that combination therapy is superior to monotherapy [52].

Nonpharmacological therapies that have been shown to be efficacious in the treatment of fibromyalgia include CBT and exercise. A prospective study found that a therapy package, including education, relaxation, and Qi Gong movement therapy, resulted in the significant improvement of symptoms in a cohort of 28 fibromyalgia patients with sustained relief [53]. A RCT of CBT in fibromyalgia showed significant improvement in all target variables [54]. Multiple RCTs combining education, CBT, and exercise in a multidisciplinary manner have shown improvement in fibromyalgia symptoms [44].

Cannabis and cannabinoids

Cannabis has been a known substance for millennia, but its potential as a legitimate drug has only recently been discovered over the past century [55,56]. Cannabis was first chemically synthesized in the 1940s, and only in the 1960s were the structures and stereochemistry of CBD and THC discovered [57]. The discovery of the CB1 and CB2 receptors in the 1980s has led to the development of bioassays capable of investigating cannabinoid receptors [56]. The discovery of receptors prompted the discovery of endogenous CBD receptor agonists. One such compound, anandamide was isolated in 1992 from a pig's brain [58]. Another breakthrough in the 1990s involved the discovery of cannabinoid receptor antagonists that were later discovered to be derived from cannabis itself. The discovery of cannabinoid ligands and receptors has later been termed the endocannabinoid system [59]. The past two decades of research have been focused on the development of more sensitive bioassays, to further explore the endocannabinoid system and its unexplored targets.

Marijuana is considered the most commonly used illicit drug in the USA; however, in recent years, nearly 10% of users have been using marijuana for medical purposes [60]. An anonymous online questionnaire found that among 2774 participants recruited through social media, 46% reported substituting cannabis for prescription drugs, including narcotics/opioids, anxiolytics/benzodiazepines, and antidepressants [61]. As of 2020, 33 states have approved medical marijuana programs, among them several states have programs that approve low THC/high CBD products for medical use [62]. As more states shift toward a more lenient medical marijuana policy, a better understanding of marijuana's medical applications is necessary.

Current indications for cannabis use

Cannabis has been used for various medical conditions. A recent systematic review determined that there is moderate-quality evidence for the treatment of pain with cannabis and low-quality evidence for the treatment of nonpain symptoms, such as nausea and vomiting, due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome [63].

Not all types of pain show a similar response to cannabis. Cancer-related chronic pain showed the greatest improvement when used at midrange doses, whereas acute pain and spasticity showed mild to no improvement [64,65]. A review of Cannabis guidelines by the Canadian Agency for Drugs (CADTH) showed that the majority of guidelines recommended cannabis for neuropathic pain, while other pain syndromes were mentioned as a consideration [66]. A systematic review of 104 studies showed that the use of cannabis for chronic noncancer-related pain is unlikely to be effective [67]. A small qualitative study reported pain reduction and decreased drowsiness post spinal cord injury as compared to other medications [68]. A systematic review showed limited evidence for the effectiveness of cannabinoids over prescription drugs or placebo, for the treatment of chronic pain due to rheumatic diseases, such as fibromyalgia, RA, and back pain [69]. Cannabis's effect on pain has a unique effect on patient well-being, unlike other pain relief remedies, described by patients as a restored self-regaining of one's sense of self [70].

A recent retrospective study of tertiary care patients using cannabis for chronic pain, described a higher prevalence of worst pain and decrease in function (social isolation, psychosocial domains, depression, and anxiety) at baseline among people who used cannabis over time, among other pain medications. The study also stated that the self-reported use of cannabis did not predict any changes in pain or other indicators, such as psychological function based on cannabis used [71].

Cannabis is also used for nonpain syndromes, such as obesity, anorexia, emesis, as well as neurological diseases, such as MS, Parkinson's disease, Huntington's chorea, Alzheimer's disease, Tourette's syndrome, and epilepsy and psychological diseases, such as bipolar disorder, schizophrenia, PTSD, depression, anxiety, and insomnia. Other chronic diseases have also been considered for cannabis treatment such as asthma, cardiovascular, glaucoma, cancer, and chronic inflammation [8]. A systematic review of medical cannabis use for psychiatric and movement disorders, showed a lack of substantial evidence for use in ALS and dystonia. Other trials were deemed to be of low quality by the Cochrane risk bias tools and showed an indefinite conclusion on the efficacy of treatment [72]. Despite widespread advocacy for cannabis use in other medical conditions, the clinical evidence to suggest the benefit of cannabis treatment is lacking [60,73].

Side effects

The use of marijuana for medicinal purposes is not without risk [74,75]. Risks associated with short-term use of marijuana range from short-term memory impairment and altered judgment to psychosis and paranoia [76]. Long-term use has been implicated with addiction, altered brain development, chronic bronchitis, and has been shown to be linked to triggering and worsening chronic psychosis and schizophrenia [76]. When a cohort of patients using cannabis for chronic pain was followed for a year, no difference was found between cannabis patients and control for adverse events [77]. Different medical conditions have shown to have different safety profiles with regard to cannabis use. For example, cannabinoids showed a higher risk of adverse events in the treatment of MS [78]. In this study of MS patients, medical cannabis and CBD-derived products produced different side effect profiles. CBD showed a better side effect profile, such as tiredness, diarrhea, and the change of appetite and weight, when studies were compared for other drugs for epilepsy, such as benzodiazepines, and other antiepileptics [79]. Cannabis has been largely associated with psychiatric symptoms. In a large multicenter case–control study, cannabis with higher THC and a low CBD concentration played a role in an increased risk of developing a psychiatric condition such as schizophrenia [80,81]. Other studies suggest that CBD has a protective role in the negative THC effect on hippocampal-dependent memory [82]. As a pharmaceutical medication, CBD predominant drugs showed side effects, including increased liver enzymes and drug–drug interactions among other cannabis-prevalent side effects, such as sedation and insomnia [83]. Other notions regarding CBD side effects include the option that THC contaminants in unregulated products might be the causing factor [84].

Cannabidiol

Cannabinoids, through their receptors, exert their effects by regulating synaptic neurotransmission [85]. These include both excitatory and inhibitory circuits that can lead to different consequences based on their location. Cannabinoid receptors and enzymes that both synthesize and degrade endocannabinoids are found throughout descending pain pathways, contributing to their association as an analgesic [86]. Out of more than 140 pharmacologically active cannabinoids, the two most relevant ones are THC (delta-9- tetrahydrocannabinol) and CBD [8]. THC is known as the psychotropic cannabinoid versus CBD that has a lower affinity to CBD receptors and is nonpsychoactive [87].

CBD products come in various forms. There are currently three FDA-approved cannabinoid-derived drugs on the market [88]: Epidiolex, a CBD-only extract is used for the treatment of severe forms of epilepsy (Lennox-Gastaut syndrome and Dravet syndrome); Nabiximols (Sativex), a marijuana extract containing equal amounts of THC and CBD, approved for the treatment of neuropathic pain and other MS-related ailments; and Dronabinol, synthetic THC used as an antiemetic [89]. Despite FDA approval, CBD drugs have shown in a recent review to have higher percentages of adverse effects than previously reported [90], possibly due to the extraction process and the inability to accurately predict the ratio of components in the extracts. Marijuana extracted oils can come from various parts of the marijuana plant (seeds, flowers, etc.) and have varying levels of CBD, with hemp/CBD oils having the highest concentration of CBD for medicinal purposes [91]. Some of the considerations when choosing a high-quality CBD oil should be to verify a low level of THC [91].

Pharmacokinetics and pharmacodynamics

Pharmacokinetics of CBD vary based on the different routes of administration, such as smoking, oral, mucosal, rectal, transcutaneous, and intravenous. Inhalation is the most common route and has a delayed THC peak concentration as compared to intravenous. Inhalation was also shown to be more effective for neuropathic pain when THC concentrations were lower than 10% [65]. The oral route has a slower absorption. Transcutaneous routes avoid first-pass metabolism and have shown tenfold higher permeability rates of CBD as compared to THC. The benefits of transcutaneous patches can lower the necessity for frequent dosing and have less abuse potential. Rectal administration shows the highest bioavailability and absorption due to decreased first-pass metabolism [92].

Cannabis treatment in fibromyalgia

The use of cannabis-derived treatments in fibromyalgia and rheumatic diseases has been the subject of considerable interest in recent years and as well as the subject of a number of clinical and scientific reviews [93,94]. Because fibromyalgia patients are often treated with a multidisciplinary approach, cannabinoids are emerging as a trend alongside the more traditional pharmacological and nonpharmacological options. Clinical data for cannabinoid treatment of fibromyalgia is scarce, though preclinical data support a molecular basis for the analgesic effects of cannabinoids [87]. While no clinical recommendations have yet been made for cannabinoids in fibromyalgia, it is thought that cannabinoids can affect pain perception, and they have also been shown to exert immunomodulatory effects [87]. Though the molecular biology and pharmacology of cannabinoids have been described, cannabinoid treatment of fibromyalgia is still exploratory and may present treatment dilemmas for clinicians [87].

Patient use characteristics

A significant number of patients with a verified diagnosis of fibromyalgia suffering from chronic pain, may seek pain relief from medical cannabis or synthetic cannabinoids. Despite the lack of clear guidelines for cannabinoid use, in a sample of 457 patients in Canada, referred to a tertiary care pain center for fibromyalgia, overall self-reported prevalence of cannabinoid use was 13%, with 80% using herbal cannabis, 24% using prescription cannabinoids, and 3% using both [95]. The diagnosis of fibromyalgia could be confirmed in 302 (66%) patients. The study authors warned of possible negative psychosocial implications of self-medication with herbal cannabis, and also suggested that some patients may use the diagnosis of fibromyalgia dishonestly to justify using herbal cannabis [95].

A 2009 retrospective study in Washington State found that out of 139 patients with valid medical records and legal access to medical cannabis, 19 patients (14%) had fibromyalgia [96]. More than one pain syndrome was present in a majority of these patients ($n = 123$, 88%). Yet, despite comorbidities and concurrent diagnoses, fibromyalgia patients have reported improved quality of life measures with cannabis use. A 2011 telephone survey of 56 patients diagnosed with fibromyalgia, according to the ACR criteria found higher mental health component summary scores on the Short Form [36] Health Survey in cannabis users ($n = 28$) than nonusers [97]. This suggests that while many fibromyalgia patients suffer from multiple medical conditions, cannabis use may have a positive impact on their overall quality of life.

In a sample of 5452 patients prescribed cannabinoid medication in Manitoba, Canada, 34% ($n = 1894$) had fibromyalgia, not excluding concomitant conditions [98]. Fibromyalgia patients had the lowest rates of cannabinoid discontinuation, followed by patients with osteoarthritis and substance use disorders. Of the three prescribed agents – nabilone (Cesamet®), dronabinol (Marinol®), and nabiximols (Sativex®) – nabilone was the most common agent. Patients were least likely to be taking nabiximols and more than twice as likely to discontinue treatment with nabiximols, probably due to its higher cost and lack of insurance coverage [98]. With the legalization of recreational cannabis in Canada and other countries, whether fibromyalgia patients continue or discontinue cannabinoid treatments may depend on medication availability as well as overlap with other disease populations.

Randomized controlled clinical trials

Cannabis and cannabinoid treatment have been investigated for a wide variety of diseases, but high-quality evidence for the use of cannabinoids in the treatment of fibromyalgia is limited [99]. Several RCTs have been conducted with cannabinoids for chronic noncancer pain, including in fibromyalgia patients [100]. RCTs of cannabinoids have been conducted in conditions, such as nausea and vomiting from chemotherapy, chronic pain, spasticity due to MS, HIV/AIDS, sleep disorders, psychiatric disorders, and glaucoma [63]. Thus far, at least two RCTs have been conducted with fibromyalgia patients, and these were evaluated by recent systematic reviews and meta-analyses [67,101]. These two small RCTs were conducted with nabilone in fibromyalgia patients and were judged to have a moderate risk of bias [102]. No RCTs to date have been conducted with herbal cannabis or plant-based cannabinoids. This is probably due to the scarcity of data; systematic reviews have yet to provide a tabular GRADE summary (Grading of recommendations and assessment, development, and evaluation) regarding cannabinoids for fibromyalgia.

The first randomized, double-blind, placebo-controlled trial of cannabinoids for fibromyalgia was conducted in 2008, investigating the use of nabilone (Cesamet, USA) in the outpatient rehabilitation hospital setting [103]. In this study, the nabilone treatment group ($n = 20$) showed significant decreases in visual analog scale for pain, fibromyalgia impact questionnaire (FIQ), and anxiety. There were no significant improvements in these measures in the placebo group and more side effects in the treatment group. A subsequent crossover study with active control design found nabilone (0.5 mg) superior to amitriptyline (10 mg) for improving sleep quality in fibromyalgia patients with chronic insomnia [104]. No significant improvements in pain, mood, or quality of life were observed in the nabilone group and mild to moderate adverse events (e.g., dizziness, headache) were more frequent in the nabilone group than in the active control group. As noted above (*see above section*), nabilone is a THC analog, but to our knowledge, no similar trials investigating CBD analogs in fibromyalgia have yet been conducted.

In the context of chronic neuropathic pain, the quality of evidence for the use of cannabis-derived medicines has been judged to be low [101]. Meta-analyses have cited a small study size as a major issue, along with possible publication bias, indirectness with respect to the patient population, and other methodological issues [101]. Most RCTs conducted included patients who were previous cannabis users. This may raise concern as to the validity of these results when applied to cannabis-naive patients.

Recent observational studies and emerging evidence

A number of recent observational studies, have attempted to characterize the regional demographic information and medication use characteristics among fibromyalgia patients pursuing treatment with medical cannabis. Examples of variables measured in these studies include: time since diagnosis, duration and frequency of consumption, and type of cannabis product (i.e., smoked, vaporized, or oil-based) [105]. In a single-center, prospective observational study of 102 consecutive fibromyalgia patients, it was found that adding treatment with cannabis oil extracts to baseline analgesic treatment led to significant improvements in the FIQ and Pittsburgh Sleep Quality Index, in 44% and 33% of patients, respectively [106]. Despite such observations, the impact of cannabis use among fibromyalgia patients can be difficult to quantify or control, as cannabis use may influence the outcomes of concurrent studies conducted in these patients [107]. It is also important to note that while recent studies suggest cannabis use in fibromyalgia patients is common, there may be significant regional differences that would make generalizing these results problematic. In light of the above epidemiological data regarding regional differences in the diagnosis and treatment of fibromyalgia, increased clinician awareness may be necessary to ensure meaningful research outcomes in the case of medical cannabis and cannabinoids.

In Israel, anonymous internet-based questionnaires have suggested that the consumption of medical cannabis among fibromyalgia patients is quite common [108]. Smaller clinical cohorts of fibromyalgia patients in this region have also reported favorable effects of medical cannabis treatment [109]. In a larger cohort study ($n = 367$) with a 6-month follow-up period ($n = 211$), a retrospective

analysis showed that medical cannabis products were generally safe and effective [110]. Pain intensity was also reduced from a median of 9.0 at baseline to 5.0 (scale of 0–10), 81.1% achieved treatment response, and common adverse effects included: dizziness (7.9%), dry mouth (6.7%), and gastrointestinal symptoms (5.4%). Quality of life measures showed improvement from baseline whether a diagnosis of fibromyalgia was primary or secondary to other conditions. Several important limitations of this study were noted, including its observational nature, possible nonresponse bias, lack of verified fibromyalgia diagnosis, lack of control group, and heterogeneity of cannabis strains and products.

In addition to the above observational evidence, a recent highly controlled crossover study of inhaled vaporized pharmaceutical grade cannabis in 20 female chronic pain patients with fibromyalgia, pain parameters were measured along with THC and CBD plasma concentrations for 3 h after single inhalation [111]. Three cannabis varieties with known quantities of THC and CBD were tested against a placebo variety with no THC or CBD. This study found that none of the active treatments affected spontaneous pain scores more than the placebo preparation. Significant analgesic effects were observed exclusively in the evoked pressure pain model and were limited to THC-containing products.

Patient-provider dynamics

Despite the lack of rigorous studies, medical marijuana is perceived by many patients with chronic pain to be a viable treatment option, so clinicians may encounter cannabis in settings ranging from primary care to subspecialty centers [75,112]. Providers may choose to prescribe cannabis products with the hope of avoiding the addictive nature of opioids or to discourage their use in favor of more specialized pain management programs or rehabilitation strategies [113]. Though not specific to the isolated diagnosis of fibromyalgia (and beyond the scope of this review), the online poll for an illustrative clinical case of a woman with chronic pain recorded that out of 3827 responses, 70% indicated that they would choose to prescribe medical marijuana, while 29% would discourage its use [113]. Such treatment dilemmas undoubtedly can and do occur for clinicians in the setting of pain management for fibromyalgia patients, as both patients and providers are becoming more aware of the option to prescribe cannabis products.

Over the past decade, cannabis-derived medicines for the treatment of chronic neuropathic pain have been the subject of considerable interest and debate among patients and providers. Since the introduction of Epidiolex for Dravet and Lennox-Gastaut syndromes by the US Food and Drug Administration in 2018, many patients and providers may negotiate trying CBD oils. However, there are currently no specific recommendations or quality considerations for the use of CBD oils in fibromyalgia, beyond the general discussion of pharmacological properties and medicolegal issues [91].

Conclusion

Fibromyalgia is hallmarked by CWP accompanied by decreased sleep quality, fatigue, and depression including a plethora of accompanying symptoms and comorbidities. It is associated with high costs, loss of productivity, and reduced quality of life in up to 10% of the general population. There are no determinant tests, and the diagnosis remains elusive. It is associated with comorbid psychiatric diagnoses in up to 60% of the cases, which may affect the selection of therapy. Diagnosis takes two years on average, and though treatments exist, only physical activity has strong evidence suggesting its efficacy; most patients continue to experience symptoms to some degree.

Both THC and CBD have been investigated for their efficacy in chronic pain [69]. Several decades of clinical data support the short-term use of cannabis for the treatment of neuropathic pain. During that time, a multitude of randomized double-blinded, placebo-controlled trials has demonstrated significant pain relief over placebo with results and tolerability similar to current pharmacological therapies [6]. Cannabis and its derivatives have also been of interest in the treatment of fibromyalgia and other rheumatic diseases in recent years. However, a 2018 systemic review and meta-analysis found only 7 studies examined cannabinoids and fibromyalgia, and the evidence was deemed to be limited [114]. Additionally, according to a 2019 position statement by the Canadian Rheumatology Association, the evidence for cannabinoids in the treatment of rheumatological disease has been inconclusive [115]. As

the legal status of cannabis and the clinical database continues to evolve, more evidence surfaces and is expected to further rise to describe the efficacy of cannabis in the treatment of fibromyalgia.

Evidence for cannabis use in fibromyalgia is limited; and however, with increasing legalization and availability of cannabis and cannabinoid products, more data are collected on its use in patients. Surveys suggest that a significant proportion of fibromyalgia patients use cannabis for pain alleviation; however, this association could also be confounded with the plethora of comorbidities associated with fibromyalgia. The quality of evidence is limited to mostly retrospective trials. A large proportion of patients report improvement in both pain and quality of life with the use of cannabis and CBD products. RCT data are limited and possibly biased; however, the data do suggest a significant reduction in pain and associated symptoms. RCTs also exist to highly support the use in other chronic pain conditions.

The use of cannabis and CBD in fibromyalgia is not without risk. Studies on users of cannabis found a higher incidence of psychosis and schizophrenia as well as associated with other psychiatric disorders. It is also associated with memory impairment, developmental and cognitive delays, particularly in younger patients. Other side effects may be more specific to conditions studied and require further attention. This should affect the selection of the population indicated for the treatment and limit its use to patients who are likely to see more benefit than harm. These risks warrant a clinical prescription for the use of cannabis to defer adverse events and risks of addiction [116]. Patients should always be made aware of the risks prior to prescription [115].

The current evidence for the use of cannabis and its derivatives in chronic pain conditions and fibromyalgia are promising and present a new approach to treatment. They are likely to be more effective when combined with physical activity, education and psychological support, and therapy. Further research is required to elucidate the patient population that is likely to benefit the most from this therapy, and the ideal combination of therapies.

Practice points

- Fibromyalgia is characterized by chronic widespread pain with sleep derangements, fatigue, and often, psychiatric comorbidities, including depression and anxiety. It is diagnosed clinically in the absence of other organic causes, a process that takes 2 years on average.
- Despite the prevalence of fibromyalgia, the understanding of its pathophysiology is vague; several treatments have some efficacy, though only physical activity has high quality evidence to support it, and most patients continue experiencing some symptoms.
- Cannabis and CBD have several indications in chronic pain syndromes with good evidence to support them. There is some evidence to support their use in fibromyalgia, though the evidence level is not high.
- With the increased availability and legality of marijuana for personal and medicinal use, surveys show a high proportion of fibromyalgia patients self-medicate with cannabis, with good results.
- Evidence shows that cannabis does not only treat chronic pain, but significantly improves the quality of life in fibromyalgia.

Research agenda

- Further understanding of the pathophysiology of fibromyalgia is required to target specific pathways with novel treatment options.
- There is a signal to suggest good efficacy from cannabis use in fibromyalgia; however, the quality of evidence is low and well-designed RCTs are required to elucidate the magnitude of benefit patients can derive.
- Cannabis use is not without risks, and those need to be further elucidated in fibromyalgia patients to derive appropriate indications and careful patient selection.

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