

Cannabis Use in Fibromyalgia

M. Farré*, A. Farré**, J. Fiz†, M. Torrens‡

*Clinical Pharmacology Unit, Germans Trias i Pujol University Hospital—IGTP, and Human Pharmacology Unit, Hospital del Mar Medical Research Institute—IMIM, and Autonomous University of Barcelona, Barcelona, Spain

**Dual Disorder Unit, Addiction Program, Institute of Neuropsychiatry and Addiction—INAD, and Hospital del Mar Medical Research Institute—IMIM, Barcelona, Spain

†CEDIR, Center for Diagnosis and Rehabilitation, San Martín Santa Fe, Argentina

‡Addiction Program, Institute of Neuropsychiatry and Addiction—INAD, and Hospital del Mar Medical Research Institute—IMIM, Barcelona, Spain

SUMMARY POINTS

- This chapter focuses on the cannabis and fibromyalgia and begins with the diagnosis and treatment of this condition.
- Therapy includes nonpharmacological and pharmacological treatments.
- Some drugs have demonstrated efficacy in randomized controlled trials (pregabalin, duloxetine, milnacipran, amitriptyline, serotonin selective reuptake inhibitors, and cyclobenzaprine).
- Cannabis products are frequently used in patients with fibromyalgia. Different surveys showed that most of the patients who tried medical marijuana found it to be effective or very effective for the therapy of symptoms of the condition.
- Evidence of efficacy is based on some noncontrolled studies and two randomized-controlled clinical trials using oral nabilone for the treatment of pain and sleep difficulties in fibromyalgia patients.
- Nabilone appears to have beneficial effect with significant reduction in pain and functional improvement, and it is well tolerated. Nabilone is more effective than amitriptyline in improving sleep in fibromyalgia.
- More studies are needed to evaluate the efficacy and safety of cannabinoids in fibromyalgia.

KEY FACTS OF FIBROMYALGIA

- Fibromyalgia is a chronic disorder characterized by widespread pain and tenderness, often accompanied by fatigue, memory problems, and sleep disturbances.
- The origin of fibromyalgia is unknown but it seems to be related to a sensitization of the central nervous system.
- The diagnosis of fibromyalgia is based on clinical symptoms, and routine laboratory and diagnostic tests are normal.
- There is no specific treatment for fibromyalgia. Nonpharmacological and pharmacological therapies could help patients.
- Some drugs are often used in the treatment of fibromyalgia pain. Three of them have been approved for this indication (pregabalin, duloxetine, and milnacipran).
- Cannabinoids by oral or smoked route can be useful to alleviate pain in fibromyalgia. However, more studies are needed in order to recommend their use.

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AEA	Anandamide
CB1/CB2	Cannabinoid receptor 1 and 2
CEDS	Clinical endocannabinoid deficiency syndromes

CNS	Central nervous system
EMA	European Medicines Agency
FDA	Food and Drug Administration
FIQ	Fibromyalgia impact questionnaire
GABA	Gamma-aminobutyric acid
LSEQ	Leeds sleep evaluation questionnaire
RCT	Randomized clinical trial
SR-MA	Systematic reviews with metaanalysis
SSNRI	Selective serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressants
THC	Δ^9 -Tetrahydrocannabinol

INTRODUCTION

Fibromyalgia

Fibromyalgia is a chronic condition characterized by widespread pain and tenderness. It is the second most common rheumatologic disorder and approximately 2–8% of the world's population meets the 1990 and 2010 American College of Rheumatology (ACR) diagnostic criteria. Fibromyalgia is more common in women and can appear at any age with a similar worldwide prevalence. Most patients have had a previous medical history of chronic pain throughout the body or chronic pain experienced in their first-degree relatives. Roughly 10–30% of patients with fibromyalgia meet criteria for other chronic pain disorders such as osteoarthritis, rheumatoid arthritis, and lupus (Rahman, Underwood, & Carnes, 2014).

As in most illnesses, fibromyalgia has a genetic component, and some studies have focused on specific genetic polymorphisms associated with the risk of developing this disorder. Findings related to polymorphisms involved in pain neurotransmission, essentially those concerning serotonin receptors and transporters, and dopamine receptors, are, however, contradictory. In addition, environmental factors play a role in triggering development of the illness. It is known that infections (Epstein–Barr virus infection, hepatitis C, parvovirus infection, and Lyme disease) and psychological stress contribute to the precipitation of this condition (Clauw, 2014).

The pathophysiological bases for fibromyalgia pain are related to a sensitization of the central nervous system (CNS) which amplifies the peripheral nociceptive inputs and maintains chronic pain. Patients with fibromyalgia feel pain in conditions that nonsufferers perceive as touch, this signifies that the former have problems with augmented pain or sensory processing in the CNS. For this reason, they display diffuse hyperalgesia (increased pain from painful stimuli) and/or allodynia (pain from nonpainful stimuli). There are, however,

no abnormalities in the region of the body where pain is experienced. A number of factors are related with an individual's sensitivity to pain. The neurotransmitters involved in pain control are also known to control other functions such as mood, fatigue, memory, and sleep, often altered in the illness. To date, it has been suggested that endogenous opioidergic activity may be normal or even increased while there is decreased activity in the endogenous serotonergic and noradrenergic systems. In addition, the glutamatergic system is also involved in the pathogenesis of fibromyalgia. Recent findings suggest an imbalance in the levels of the neurotransmitters that affect pain and sensory transmission: high levels of neurotransmitters increase pain transmission and/or low levels of neurotransmitters decrease it. Neuroimaging studies have contributed to demonstrating the neurotransmitter hypothesis, and to finding the structures implicated in fibromyalgia such as the insula. Moreover, sensitivity to different stimuli such as heat, cold, electrical stimuli, and auditory tones is also augmented (Kuttikat & Shenker, 2013; Clauw, 2014, 2015; Rahman et al., 2014)

The symptoms of fibromyalgia include musculoskeletal pain in various groups of muscles, especially in the proximal shoulder girdle muscles, which is poorly localized, of severe intensity, and difficult to ignore. It is present most of the day, appears every day, and for at least 3 months. Another characteristic of this disorder is the appearance of focal, triggered point tenderness in affected muscles. In addition, patients complain of fatigue, muscular weakness, sleep disturbance, mood disorders, and impairment of some cognitive domains such as concentration and alertness. Depending on the somatic and psychological symptoms, fibromyalgia can cause functional disability (Clauw, 2014; Rahman et al., 2014).

In 1999, the ACR published the classification criteria for fibromyalgia syndrome which have been used widely used in therapeutic clinical trials. These criteria had a sensitivity of 88% and a specificity of 81% in a patient population (Table e16.1). Subsequently, the ACR published in 2010 further preliminary diagnostic criteria, taking into account the relevance of somatic symptoms such as fatigue and cognitive difficulties associated with this syndrome. These new criteria developed for clinical use have a symptom severity scale which can be useful for longitudinal monitoring. One major difference is that they do not require a tender point count (Table e16.2). In addition, there is a patient self-report version (Clauw, 2014, 2015).

Routine laboratory and radiographic tests are normal, focused on excluding other diagnoses and evaluating pain generators and comorbid conditions. It is important to carry out a differential diagnosis because some symptoms can overlap with other chronic pain conditions such as headaches, facial/jaw pain, regional myofascial

TABLE e16.1 American College of Rheumatology 1990 Classification Criteria for Fibromyalgia*Criteria*

- A. History of widespread pain for at least 3 months. Pain is considered widespread when it is present at all of the following sites (b):
- the left side of the body
 - the right side of the body
 - above the waist
 - below the waist
 - in the axial skeletal (cervical spine or anterior chest or thoracic spine or low back)
- B. Pain on digital palpation in at least 11 of the 18 tender point sites; all sites bilateral (c):
- (a) For purposes of classification, patients will be said to have FMS if both criteria A and B are satisfied. The presence of a second clinical disorder does not exclude the classification of fibromyalgia
 - (b) Pain in a patient in for instance the left shoulder, right buttock, and cervical spine is generalized, according to these criteria
 - (c) Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered positive, the palpation has to be painful. “Tender points” that are only tender are not tender points

TABLE e16.2 American College of Rheumatology 2010 Preliminary Diagnostic Criteria for Fibromyalgia*Criteria*

A patient satisfies diagnostic criteria for FMS if the following three conditions are met:

1. Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 , or WPI between 3 and 6 and Symptom Severity (SS) scale score ≥ 9
2. Symptoms have been present at a similar level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain

Ascertainment

1. Widespread pain index (WPI)
 - Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Shoulder girdle (left, right); Hip (left, right); Jaw (left, right); Upper back: Lower back; Upper arm (left, right); Upper leg (left, right); Chest; Lower arm (left, right); Lower leg (left, right); Abdomen and Neck
 - Score will be between 0 and 19
2. Symptom severity (SS) scale score: fatigue, waking unrefreshed, cognitive symptoms
 - For the each of the three symptoms above, indicate the level of severity over the past week using the following scale: 0 = no problem, 1 = slight or mild problems, generally mild or intermittent, 2 = moderate, considerable problems, often present and/or at a moderate level, 3 = severe: pervasive, continuous, life-disturbing problems
 - Considering somatic symptoms in general^a, indicate whether the patient has: 0 = no symptoms, 1 = few symptoms, 2 = a moderate number of symptoms, 3 = a great deal of symptoms
 - The somatic symptoms scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general
 - The final score is between 0 and 12

^a Somatic symptoms that might be considered muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/urticaria, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

pain in the neck or back, and arthritis. Visceral pain complaints involving the gastrointestinal tract, bladder, and pelvic or perineal region are also often present (Crofford, 2013; Clauw, 2014, 2015).

Treatment of Fibromyalgia

Treatment strategies include nonpharmacological and pharmacological therapies including medicines and cannabis. It has been demonstrated that education, cognitive behavioral therapy, and exercise (passive and active) are effective in dealing with fibromyalgia with a response that usually surpasses pharmacological therapies. There is also limited evidence from a systematic review and a summary of reviews concerning the benefits

of acupuncture, homeopathy, and mind-body therapies, including hypnotherapy, biofeedback, and stress reduction (Clauw, 2014; Ablin & Buskila, 2010; Häuser, Walitt, Fitzcharles, & Sommer, 2014; Rahman et al., 2014).

Pharmacological treatment includes drugs approved by the agencies of various countries; however, a wide number of medications are used in an off-label indication (Ablin & Buskila, 2010; Häuser et al., 2014). Three drugs (pregabalin, duloxetine, and milnacipran) have been passed by the United States Food and Drug Administration (FDA) but not by the European Medicines Agency (EMA). The use of cannabinoids is described in [section cannabinoids and fibromyalgia \(p. 1095\)](#).

Taking into account the moderate efficacy of the available pharmacological therapies, drug therapy is not

mandatory in all fibromyalgia cases. Mean efficacy from systematic reviews with metaanalysis (SR-MAs) pooled data found that 19% of patients had at least a 50% reduction in pain but that 11% stopped treatment due to adverse events. It is recommended to choose the drug according to the main symptoms (pain, fatigue, and sleep disorder), physical and psychological comorbidities, and side effects. In addition, it is crucial to monitor efficacy, tolerability, and safety in order to achieve responsible prescribing practices. In most cases, treatment includes a combination of drugs with different mechanisms of action (Rahman et al., 2014).

Gabapentinoids (pregabalin, gabapentin), serotonin norepinephrine reuptake inhibitors (duloxetine and milnacipran), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) are currently prescribed as standard treatment for fibromyalgia. These options have been studied in randomized clinical trials (RCT); nevertheless, their clinical benefits remain limited for most patients (Häuser et al., 2014; Rahman et al., 2014).

Pregabalin

A gamma-aminobutyric acid (GABA) analog, that binds to an auxiliary subunit (alpha2-delta protein) of voltage-gated calcium channels in the CNS. Pregabalin is approved in Europe for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures, and for the treatment of generalized anxiety disorder (GAD) in adults. In the United States, pregabalin has the following approved indications: neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, adjunctive therapy for adult patients with partial onset seizures, fibromyalgia, and neuropathic pain associated with spinal cord injury. In the management of fibromyalgia, doses must be titrated to reach the recommended dose of 300–450 mg/day (divided in two administrations). Higher doses, such as 600 mg/day, do not confer additional benefit and are less well tolerated. Most common adverse effects are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and difficulty concentration/attention (>5% patients). The efficacy of pregabalin in fibromyalgia has been demonstrated in several RCTs and SR-MA (Moore, Straube, Wiffen, Derry, & McQuay, 2009; Moore et al., 2012a; Üçeyler, Sommer, Walitt, & Häuser, 2013; Rahman et al., 2014).

Duloxetine

A selective serotonin and norepinephrine reuptake inhibitor (SSNRI) indicated in the United States for: major depressive disorder, GAD, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, and fibromyalgia, but in Europe not approved for fibromyalgia. The recommended dose for fibromyalgia is 60 mg/day.

Nausea, somnolence, insomnia, dry mouth, constipation, decreased appetite and dizziness, and sexual dysfunction are the main side effects (>5% of patients). Its efficacy in fibromyalgia has been demonstrated in several RCTs and SR-MAs (Häuser, Bernardy, Üçeyler, & Sommer, 2009; Häuser, Urrútia, Tort, Üçeyler, & Walitt, 2013; Lunn, Hughes, & Wiffen, 2014; Rahman et al., 2014).

Milnacipran

It is an SSNRI more selective for norepinephrine uptake. The recommended dose is 100 mg in two divided daily doses. Common side effect are nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, palpitations, dry mouth, and hypertension (>5% patients). Its efficacy in fibromyalgia has been demonstrated in several RCTs and SR-MAs (Häuser et al., 2009, 2013; Derry, Gill, Phillips, & Moore, 2012; Rahman et al., 2014).

Amitriptyline

Amitriptyline 10–50 mg daily is used in fibromyalgia to treat sleep problems and fatigue as an off-label indication. Common (>5% frequency) side effects include dizziness, headache, weight gain, hypotension, somnolence, sexual dysfunction, and dry mouth. Its efficacy in fibromyalgia has been demonstrated in several RCTs and SR-MAs (Häuser et al., 2009, 2014; Moore et al., 2012a,b).

Selective Serotonin Reuptake Inhibitors

There are some studies that found some evidence in favor of fluoxetine (12–80 mg/day), paroxetine (20–60 mg/day), and citalopram (20–40 mg/day) (Häuser et al., 2009, 2014; Rahman et al., 2014).

Cyclobenzaprine

A muscle relaxant marketed in the United States, but unavailable in most European countries. The recommended dose is 5 mg 3 times a day. Most common side effects were drowsiness (38% of patients), dry mouth (24%), and dizziness (10%). Its use in fibromyalgia is based on six RCTs (with small samples) and a SR-MA (Tofferi, Jackson, & O'Malley, 2004; Häuser et al., 2014).

Gabapentin

It is similar to pregabalin, and with approved use for adjunctive therapy of epilepsy and treatment of peripheral neuropathic pain/postherpetic neuralgia in adults. The recommended dose for pain varies between 1200–2400 mg/day (maximum 3600 mg/day). Gabapentin has shown similar efficacy and adverse effects as pregabalin in fibromyalgia, but there is less evidence from RCTs and SR-MA (Üçeyler et al., 2013; Moore, Wiffen, Derry, Toelle, & Rice, 2014).

Strong opioids (tramadol, oxycodone) and nonsteroidal antiinflammatory drugs, either as a prescription or on-demand, are not recommended as a strategy in

TABLE e16.3 Drug Classes That Failed to Show Superiority Over Placebo in Reducing Fibromyalgia Syndrome Symptoms

Antidepressants (sertraline, venlafaxine)
Antiviral agents (valacyclovir)
Anxiolytics (alprazolam, bromazepam)
Dopamine agonists (pramipexole, ropinirole, terguride)
Hormones (calcitonin, dehydroepiandrosterone, prednisone)
Hypnotics (zolpidem)
Interferons
Ketamine (intravenous)
Local anesthetics (lidocaine, intravenous)
Neuroleptics (ritanserin, quetiapine)
Opioids (oxycodone, tramadol)
Serotonin receptor antagonists (tropisetron, ondansetron)
Sodium oxybate (gamma-hydroxybutyrate)

Based on data from [Hauser et al. \(2014\)](#).

fibromyalgia because of the lack of evidence from published RCTs and the potential risk of side effects ([Häuser et al., 2014](#)).

A number of other drugs have been studied for treating fibromyalgia, none of them; however, show any superiority with respect to placebo ([Table e16.3](#)). Recent research, based on few studies with small sample sizes, has shown efficacy of nabilone for pain and sleep disturbance (see [section randomized controlled clinical trials, p. e164](#)), growth hormones for pain and fatigue, and quetiapine or naltrexone to reduce pain and depression ([Häuser et al., 2014](#)).

CANNABINOIDS AND FIBROMYALGIA

Biological Basis

The endogenous cannabinoid system mainly includes the cannabinoid receptors CB1 and CB2, the ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and their metabolic enzymes (fatty acid amide hydrolase 1 or FAAH, and monoacylglycerol lipase or MAGL). CB1 is the most abundant G protein-coupled receptor expressed in the brain, in nonneuronal cells such as adipocytes and hepatocytes, and in musculoskeletal tissues. CB2 is principally associated with immune cell function, although it may also be expressed in the CNS. Endocannabinoids have the particularity of act as retrograde messengers by binding to presynaptic CB1 receptors. Cannabinoids are neuromodulators of the glutamate, GABA, serotonin, dopamine, norepinephrine and acetylcholine release ([Pacher, Bátkai, & Kunos, 2006](#); [McPartland, Guy, & Di Marzo, 2014](#)). The endocannabinoid system and its role are extensively reviewed in other chapters.

The endocannabinoid system has a number of physiological actions. It is implicated in the modulation of embryological development, neural plasticity, neuroprotection, immunity and inflammation, apoptosis

and carcinogenesis, pain and emotional memory, stress response, neuroendocrine regulation and cognitive functions, alimentary behavior (hunger, feeding), and metabolism.

Various authors ([Russo, 2008](#); [Smith & Wagner, 2014](#)) have suggested that some diseases are associated with the suboptimal functioning of the endocannabinoid system. Known collectively as clinical endocannabinoid deficiency syndromes (CEDS), these dysfunctions have been proposed as being responsible for migraine, fibromyalgia, irritable bowel syndrome, and related conditions. It has been suggested that interventions enhancing the endocannabinoid system—upregulating cannabinoid receptors, increasing ligand synthesis, and inhibiting ligand degradation—could be useful for CEDS ([McPartland et al., 2014](#)).

[Kaufmann et al. \(2008\)](#) evaluated the plasma concentrations of catecholamines, cortisol AEA, and neutrophil function in 22 patients with primary fibromyalgia and 22 age- and sex-matched healthy controls. The results showed that the fibromyalgia patients had significantly higher norepinephrine and AEA plasma levels than controls. Adhesion and phagocytosis capabilities of neutrophils correlated positively with AEA plasma levels.

Studies on the Use of Cannabinoids in the Treatment of Fibromyalgia

There is a limited number of clinical studies assessing the efficacy of cannabinoids (natural or synthetic) in the treatment of fibromyalgia symptoms. Most evidence comes from surveys and observational studies with a few RCTs ([Lynch & Campbell, 2011](#); [Lynch & Ware, 2015](#)).

Surveys

In a study carried out at the University of Washington in a regional pain clinic ([Aggarwal et al., 2009](#)), the retrospective chart review of a total of 139 patients using medicinal cannabis showed that 19% were taking it for fibromyalgia pain.

A survey was performed in pain clinics in Germany where medicinal dronabinol was prescribed for pain in addition to the current treatment ([Weber et al., 2009](#)). Complete data were collected from 124 patients suffering from refractory central neuropathic pain and fibromyalgia. The subjects participated in a standardized, retrospective, telephone interview survey that included changes in pain intensity using the Numeric Rating Scale (NRS), the Pain Disability Index (PDI), the Medical Outcomes Short-Form (SF-12), the Quality of Life Impairment by Pain (QLIP), Hospital Anxiety Depression Scale (HADS), and concomitant pain medication. In the 32 fibromyalgia patients included, mean pain intensity prior

to dronabinol administration was on average 7.9 ± 1.5 units, which was reduced to 4.4 ± 1.5 units during/after THC-treatment. On average, maximum pain intensity was recorded at 9.3 ± 1.1 units, prior to dronabinol and 6.1 ± 2.1 thereafter. Other results of the survey were presented collectively from all the patients: opioid doses were reduced, and patients perceived THC therapy as effective, with relatively good tolerability (25% did not tolerate the treatment).

The prevalence of cannabinoid use in 457 fibromyalgia patients who had been referred to a tertiary care pain center was assessed in Canada (Ste-Marie, Fitzcharles, Gamsa, Ware, & Shir, 2012). The study included a retrospective chart review of all the patients. It was found that 1 in 8 ($n = 59$, 13%) were using cannabis, of these 80% consumed herbal cannabis (marijuana), 24% took prescription cannabinoids ($n = 13$ nabilone, and $n = 1$ dronabinol), and 3% took both herbal cannabis and prescription cannabinoids. All 47 patients using herbal cannabis declared smoking marijuana between 0.5 and 6 g/day, and 34 (72%) reported the use of 1 g or less a day. The clinical data of the 59 subjects employing cannabinoids were compared with the 308 nonusing patients. The cannabinoid users were more frequently male, took more opioids, and presented greater drug-seeking behavior. A subanalysis of the sample, taking into account only those reporting herbal cannabis administration (47 vs 410 subjects), was carried out. Herbal cannabis users presented more current unstable mental illness (36% vs 23%) and opioid drug-seeking behavior (17% vs 4%), and were more frequently male (26% vs 7%). The conclusions of the study, that herbal cannabis use is associated with negative psychosocial parameters, should be cautiously interpreted due to the design of the protocol (a retrospective medical chart review).

An online survey performed by the National Fibromyalgia and Chronic Pain Association (NFCPSA; Bener, 2014) obtained a response from 1200 of its members: 44% had tried marijuana or cannabis for their pain. Positive responses were obtained for sleep (8.4 points in a 0–10 scale), pain (8.2 points), and fatigue (6 points). 22% of the responders used marijuana on a daily basis for their pain. Most subjects did not report side effects (66%), but some described sedation (165), cognitive dulling (6%), anxiety (5%), weight gain (4%), and addictive craving (3%).

A recent survey from the National Pain Foundation showed that medical marijuana may top currently available medicines for treating fibromyalgia (Anson, 2014). The survey, which was conducted online, asked more than 1300 patients with fibromyalgia to rate the effectiveness of the treatments that they had used. Medical marijuana was compared with the three drugs approved by the FDA for fibromyalgia: milnacipran (Savella), pregabalin (Lyrica), and duloxetine (Cymbalta) (Table e16.4).

TABLE e16.4 Effectiveness of Some Pharmacological Treatments Rated by Fibromyalgia Patients in an Online Survey ($n = 1300$)

Drug	Very effective (%)	Helps a little (%)	Does not help at all (%)
Pregabalin (Lyrica)	10	29	61
Duloxetine (Cymbalta)	8	32	60
Milnacipran (Savella)	10	22	68
Medical marijuana	62	33	5

Patients rated the efficacy as "Very effective", "Helps a little," and "Does not help at all". Results are presented as percentages [based on data from Anson (2014)].

Only 8% of the patients that tried duloxetine, and 10% that tried pregabalin or milnacipran, found the drugs to be "very effective" for managing symptoms of the disorder. Over 60% of the patients reported that each of three drugs "does not help at all." On the other hand, 62% of the patients who tried medical marijuana found it to be "very effective." Another 33% said it "helps a little," and 5% felt that using cannabis for fibromyalgia "does not help at all."

Nonrandomized and Noncontrolled Clinical Trials

In Spain, Fiz, Durán, Capellà, Carbonell, and Farré (2011) conducted a case-control study in patients suffering from fibromyalgia, some were cannabis users ($n = 28$), and others not ($n = 28$). The participants completed a series of quality of life questionnaires including the Fibromyalgia Impact Questionnaire (FIQ), the Pittsburgh Sleep Quality Index (PSQI), and the Short Form 36 Health Survey (SF-36). They were further asked to record the perceived benefits of cannabis on a range of symptoms (pain, stiffness, relaxation, drowsiness, and well-being) using 100 mm VAS scales (VAS) prior to and at 2 h of cannabis consumption. Based on a list of symptoms, the occurrence and frequency of side effects were evaluated. Demographics and clinical variables were similar in both groups. Of the 28 fibromyalgia cannabis users, 11 (40%) reported a duration of cannabis consumption of less than 1 year, 9 (32%) between 1 and 3 years, and 8 (29%) more than 3 years. Only eight patients in the cannabis group had previously tried it recreationally. The cannabis derivate in every case was marijuana, and the route of administration was smoking (54%), oral (46%), and combined (43%). Patients employed cannabis not only to alleviate pain but for almost all the symptoms associated with fibromyalgia, and

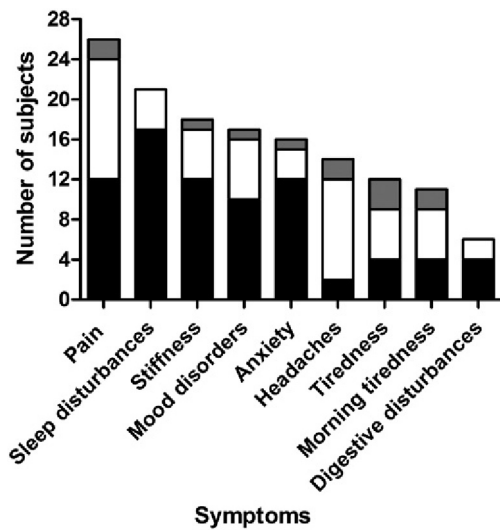


FIGURE e16.1 Symptoms and perceived relief reported by fibromyalgia patients using cannabis. Perceived relief was recorded using 5-point Likert scale (strong relief, mild relief, not change, slight worsening, great worsening). The histogram shows the number of subjects for each relief category (black color, strong relief; gray color, mild relief; white color, no change.). Source: Based on data from Fiz et al. (2011).

none reported worsening of symptoms. The proportion of patients who described strong relief ranged from 81% for sleep disorders to 14% for headache (Fig. e16.1). In relation to quality of life, only the mental health component summary score of the SF-36 questionnaire was slightly, but significantly higher, in the cannabis group than in the nonuser group. After 2 h of cannabis use, VAS scores showed a statistically significant reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence and feeling of well-being (Fig. e16.2). The

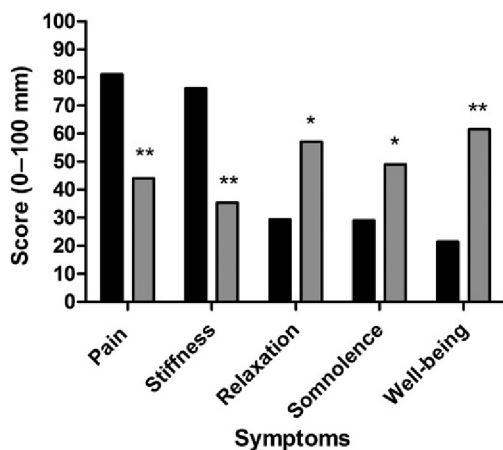


FIGURE e16.2 Perceived effects of cannabis self-administration in some symptoms (scores at baseline and 2 h after cannabis use). Perceived benefits of cannabis recorded by patients on a range of symptoms using 100-mm VAS scales before and at 2 h of cannabis consumption. Gray bars, pre-cannabis; black bars, post-cannabis. [**, $p < 0.001$; *, $p < 0.05$; with permission from Fiz et al. (2011)].

most frequent side effects were somnolence ($n = 18$), dry mouth ($n = 17$), sedation ($n = 12$), dizziness ($n = 10$), feeling high ($n = 9$), tachycardia ($n = 8$), conjunctival irritation ($n = 7$), and hypotension ($n = 6$).

In nine fibromyalgia patients, the effect of oral THC on electrically induced pain, axon reflex flare (vasodilatation), and psychometric variables was investigated (Schley et al., 2006). The study was noncontrolled, and subjects were compared before and after cannabinoid administration. The participants received a daily oral dose of 2.5–15 mg THC. Starting with 2.5 mg, the dosage was increased weekly by 2.5 mg THC, as long as no severe side effects were reported. Once a week, 24 h after the last THC medication and a day before any dose increase, an electrically induced pain was performed. The pain intensity was recorded daily by means of a numeric pain scale, from 0 (no pain) to 10 (maximum pain imaginable). In the four participants who completed the 3-month study, pain decreased on average by 67% (mean pain score difference -5.3 ± 2.3). All four experienced a pain reduction by more than 50% (mean pain score difference -2.8 ± 5). The experimentally induced pain was significantly reduced by THC at a dose of 10 and 15 mg. Daily recorded pain intensity was lowered on average from 8.1 at the beginning of the study, to 2.8 after 3 months. THC had no effect on the axon reflex flare, and no differences were found in the psychometric variables. Five of the nine participants dropped out of the study before achieving the maximum dose of 15 mg due to severe side effects (primarily sedation, dizziness, fatigue, and continuous tiredness).

Randomized Controlled Clinical Trials

In one of the few published RCTs, Skrabek, Galimova, Ethans, and Daryl (2008) carried out a double-blind, randomized, placebo-controlled clinical trial to analyze the effects of oral nabilone and placebo on pain and quality of life in patients with fibromyalgia. After 4 weeks of treatment (nabilone group = 0.5 mg once daily in week 1, 0.5 mg twice daily in week 2, 0.5 mg in the morning, and 1 mg in the evening in week 3, and 1 mg twice daily in week 4), patients who received nabilone ($n = 15$) experienced significant improvements in clinical pain, measured on a visual analog scale (-2.04 cm, $p < 0.02$), FIQ score (-12.07 , $p < 0.02$) and the 10-point anxiety scale of the FIQ (-1.67 , $p < 0.02$) in comparison to placebo. After a 4-week washout period at the end of the trial, all benefits were lost in the nabilone cohort, who returned to their baseline levels of pain and quality of life. Patients who received placebo ($n = 18$) experienced no change throughout the study. Side effects were more common in the nabilone treated subjects, compared with placebo controls at both 2 and 4 weeks of treatment. The most common side effects reported by subjects in the

nabilone group include drowsiness (7/15), dry mouth (5/15), vertigo (4/15), and ataxia (3/15). No serious adverse events appeared during the study.

A randomized, double-blind, active-control, equivalence crossover trial was carried out in fibromyalgia patients with chronic insomnia (Ware, Fitzcharles, Joseph, & Shir, 2010). The compared oral treatments were nabilone and amitriptyline (0.5–1.0 mg and 10–20 mg before bedtime, respectively). Subjects received each drug for 2 weeks with a 2 week washout period between the two treatment phases. The primary outcome was quality of sleep as measured by the Insomnia Severity Index and the Leeds Sleep Evaluation Questionnaire (LSEQ). Secondary outcomes included pain, mood, quality of life, and adverse events. A total of 31 subjects were included and 29 completed the study (26 women, mean age 49.5 years). Sleep was improved by both amitriptyline and nabilone, although nabilone was superior to amitriptyline (Insomnia Severity Index difference 3.2; 95% confidence interval 1.2–5.3). No significant differences were found in the LSEQ. No effects on pain, mood, or quality of life were observed. Preference at the end of the trial for nabilone was higher (41% of the subjects) than for amitriptyline (32%). Adverse events were mostly mild to moderate and were more frequent with nabilone. Fifty-three and ninety-one adverse events were deemed possibly or probably related to amitriptyline and nabilone therapy, respectively. Adverse events occurring in more than two subjects, and which were more common for nabilone, were dizziness ($n = 10$ subjects), nausea ($n = 9$), dry mouth ($n = 7$), drowsiness ($n = 6$), headache ($n = 4$), constipation ($n = 4$), insomnia ($n = 3$), and vomiting ($n = 3$). In the case of amitriptyline they were headache ($n = 6$ subjects), dizziness ($n = 4$), dry mouth ($n = 3$), and blurred vision ($n = 3$). The researchers concluded that “nabilone is effective in improving sleep in patients with fibromyalgia and is well tolerated. Low-dose nabilone given once daily at bedtime may be considered as an alternative to amitriptyline.”

Health Professionals’ Opinions on the Use of Cannabinoids

There are no specific studies about opinions or surveys concerning the use of cannabinoids in fibromyalgia pain. A recent online survey carried out with rheumatologists in Canada evaluated their confidence concerning their knowledge of cannabinoid molecules and mechanisms relevant to rheumatology, and their ability to advise patients about cannabinoid treatments (Fitzcharles et al., 2014b). Results showed that over three quarters of the 128 respondents lacked confidence in their knowledge with respect to cannabinoid molecules. A total of 45% of respondents believed there was no current role for cannabinoids in rheumatology patient care, and only

25% supported any use of herbal cannabis. Most of them had never previously prescribed or recommended any cannabinoid treatment (70%). Their uncertainty regarding good prescribing practices was very prevalent. The authors suggested that “Guidance is required to inform rheumatologists on the evidence regarding cannabinoids.” The results were similar to a survey that was conducted among Canadian family doctors to determine the educational needs regarding the use of cannabis for therapeutic purposes (Ziemianski et al., 2015).

Fitzcharles, Clauw, Ste-Marie, and Shir (2014a) commented recently on the increasing hiatus among public advocacies for herbal cannabis as a therapeutic agent in rheumatic conditions. Shortfalls included uncertainty of compound content, unknown dosing, recommendations not to use by inhalation, and the indicators of harm, both in the acute as well as chronic setting, and the medical evidence for efficacy and side effects. They concluded that “Taking all factors into consideration, health care professionals should currently dissuade rheumatology patients from using herbal cannabis as a therapy.”

CONCLUSIONS

In the near future, the worldwide increase of countries with authorized use of medicinal cannabis, and the augment in licenses for doctors to prescribe it, will raise the number of patients legally employing cannabis products as compassionate disease therapy.

In the case of fibromyalgia, evidence of cannabinoid use is very limited. There are only two short-term RCTs with a limited number of subjects experiencing positive results from oral dronabinol. Noncontrolled studies have shown positive effects in pain after the administration of natural cannabinoids by different administration routes. Patient surveys have reported that some of them employ cannabinoids, mainly herbal cannabis, to control pain and other symptoms in fibromyalgia.

The use of cannabinoid medicines in fibromyalgia pain must be assessed through standard scientific methods. More studies are needed to know the role of the endocannabinoid system in their pathogenesis, and to evaluate efficacy and safety of cannabinoids in fibromyalgia.

MINI-DICTIONARY

Allodynia A pain response from stimuli which do not normally provoke pain (eg, mild tactile pressure on a muscle).

Crossover clinical trial A study in which subjects receive more than one treatment, usually a sequence of two or more different treatments (or exposures).

Double-blind clinical trial A study in which neither the participants nor the researchers know which treatment the participants are taking.

Fibromyalgia A disorder characterized by chronic widespread pain, and a heightened and painful response to pressure, often accompanied by fatigue, memory problems, and sleep disturbances.

Hyperalgesia An increased pain response. Pain is more painful than it should be considering the stimuli.

Metaanalysis A statistical method for contrasting and combining results from different studies, usually randomized clinical trials, to resolve uncertainty when studies have a small number of subjects, or results from different studies do not concur.

Off-label use The use of drug agency-approved pharmaceutical drugs for different indications including an unapproved indication, an unapproved age group, unapproved dosage, and unapproved form of administration.

Randomized-controlled trial or Randomized-controlled clinical trial A type of scientific experiment in which the people being studied are randomly allocated to one (control) or other (test) of the different treatments under study. It is considered the gold standard for the efficacy evaluation of medical therapies. Sometimes the control group is placebo.

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