# Medical Cannabis for the Treatment of Fibromyalgia

George Habib, MD, MPH\*†‡ and Suheil Artul, MD§//

**Background:** Fibromyalgia is a chronic pain syndrome, characterized by chronic musculoskeletal pain, fatigue, and mood disturbances. There are nearly no data on the effect of medical cannabis (MC) treatment on patients with fibromyalgia.

**Methods:** Data were obtained from the registries of 2 hospitals in Israel (Laniado Hospital and Nazareth Hospital) on patients with a diagnosis of fibromyalgia who were treated with MC. After obtaining patient consent, demographic, clinical, and laboratory parameters were documented. All the patients also completed the Revised Fibromyalgia Impact Questionnaire regarding the period before and after MC treatment.

**Results:** Thirty patients were identified, and 26 patients were included in the study. There were 19 female patients (73%), and the mean age of the study group was  $37.8 \pm 7.6$  years. The mean dosage of MC was  $26 \pm 8.3$  g per month, and the mean duration of MC use was  $10.4 \pm 11.3$  months. After commencing MC treatment, all the patients reported a significant improvement in every parameter on the questionnaire, and 13 patients (50%) stopped taking any other medications for fibromyalgia. Eight patients (30%) experienced very mild adverse effects.

**Conclusions:** Medical cannabis treatment had a significant favorable effect on patients with fibromyalgia, with few adverse effects.

Key Words: fibromyalgia, medical cannabis, treatment

(J Clin Rheumatol 2018;00: 00-00)

F ibromyalgia is one of the most common chronic pain syndromes.<sup>1</sup> It is characterized by diffuse musculoskeletal pain, in addition to extreme fatigue and mood and sleep disturbances.<sup>1</sup> The pathogenesis of fibromyalgia is not clear. It usually affects women more than men and has a genetic preponderance.<sup>2</sup> Its prevalence in the general population is estimated to be approximately 7%, and it is more common among women than men.<sup>3</sup>

Fibromyalgia can have tremendous physical, as well as psychological, impacts on patients. For example, many patients may be unable to accomplish various tasks at work and home, resulting in physical disability, which can be accompanied by anxiety and depression. Unfortunately, in most patients, fibromyalgia is chronic, and the main treatment is pain control medications. These medications include simple analgesics, pregabalin, and opiates. For Patients with fibromyalgia may also benefit from tricyclic antidepressants, benzodiazepines, and other types of antidepressants. However, many of these medications are associated with adverse effects, which affect compliance. As a result, many patients with fibromyalgia experience continuous pain.

Cannabis is derived from the cannabis plant and is considered an illicit drug in most countries, including Israel. However, it is widely used illegally or legally in some countries where

From the \*Rheumatology Unit, Laniado Hospital, Netanya; †Faculty of Medicine, Technion, Israel Institute of Technology, Haifa; ‡Rheumatolgy Clinic and §Department of Radiology, Nazareth Hospital, Nazareth; and ||Galilee Faculty of Medicine, Bar Ilan University, Ramat Gan, Israel.

The authors declare no conflict of interest.

Correspondence: George Habib, MD, MPH, Rheumatology Unit, Laniado Hospital, Netanya, Israel 42150. E-mail: gshabib@gmail.com.
Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 1076-1608

DOI: 10.1097/RHU.00000000000000702

cannabis use is not outlawed.<sup>8</sup> The 2 main cannabis plant species are *Cannabis sativa* and *Cannabis indica*.<sup>9</sup> Most species today are a hybrid of the two, with cannabis derived from *C. sativa* designed mainly for morning or daytime use because it induces "energy" and cannabis derived from *C. indica* reserved primarily for evening or nighttime use because it induces calmness and good sleep.<sup>10</sup> The flowers of the cannabis plant contain more than 100 types of phytocannabinoids. Most research has focused on Δ-9-tetrahydrocannabinol and cannabidiol, both of which have the highest concentrations of phytocannabinoids.<sup>11</sup> There are 2 known receptors of endogenous cannabinoids (endocannabinoids): CB1 and CB2.<sup>12</sup> CB1 is mainly found in the central nervous system.<sup>12</sup> CB2 is found in different organs of the body, with its activities mainly related to the immune system.<sup>12</sup> Δ-9-Tetrahydrocannabinol is a partial agonist for the CB1 and CB2 receptors, and cannabidiol is an antagonist. Activation of CB1 results in a decrease in synaptic signals and neurological excitability.<sup>13</sup>

In recent years, cannabis had been legislated in some states in the United States for medical use, as well as in some countries in Europe. 14,15 In Israel, medical cannabis (MC) is licensed by the Israeli Medical Cannabis Agency of the Ministry of Health for patients with specific indications, including cancer with uncontrolled pain, Crohn disease with uncontrolled gastrointestinal symptoms, uncontrolled seizures, uncontrolled Parkinson disease, posttraumatic stress disorder, and unresponsive diabetic neuropathy. Requests for an MC license are submitted by the specialist taking care of the patient. Based on the recommendations of the Israeli Rheumatology Association, fibromyalgia is not included in the list of indications for MC. However, approval for MC treatment may be granted in some cases of fibromyalgia, especially for fibromyalgia patients who are also receiving treatment by other subspecialties, such as pain clinics, orthopedics (for discopathy), psychiatrists, and/or gastroenterologists (for irritable bowel syndrome). In most cases, following approval, the starting dose of MC is 20 g per month. The drug may be supplied directly to the patient every month or collected from a distribution center. Initially, the patient will be instructed in the use of MC by the supply team, and the patient may choose the mode of consumption (i.e., smoking, vaporization, oral oil drops, or a combination of these). There are 8 suppliers of MC in Israel, and the patient has the right to choose the company that supplies the MC. The patient is advised to consume the same amount of MC daily to prevent a shortage of MC by the end of the month.

There are only a few studies in the literature on the use of cannabis by fibromyalgia patients. <sup>16,17</sup> In these studies, the patients used unlicensed cannabis from different suppliers, and the studies contained no information on either the type or amount (in grams) of cannabis used. In general, the patients in these studies reported favorable effects of cannabis use. A systematic review of the use of synthetic cannabinoids in fibromyalgia (nabilone, 2 studies) found evidence (very low quality) of a greater reduction in pain and limitations in health-related quality of life in the synthetic cannabinoid group as compared with a placebo group in 1 study and better effects of synthetic cannabinoids on sleep than amitriptyline in another study. <sup>18</sup> The aim of the present study was to examine the effects of licensed MC on patients with fibromyalgia in an Israeli population.

### PATIENTS AND METHODS

This was a retrospective review of patients with fibromyalgia who were treated with MC. Data were obtained on patients with fibromyalgia from the registries of Laniado Hospital, Netanya, and Nazareth Hospital, Nazareth, Israel. All the patients met the diagnostic criteria for fibromyalgia.<sup>19</sup> The patients were contacted and asked to participate in the study.

The inclusion criteria were patients older than 18 years and being able to sign a consent form. The exclusion criteria were patients with malignancy-associated or other rheumatic diseaseassociated fibromyalgia.

All the patients signed a consent form, and the study was approved by the local ethics committee of Laniado Hospital.

After obtaining consent, demographic, clinical, and laboratory parameters were documented. Demographic data included age and sex. Clinical data included the duration of symptoms of fibromyalgia, time of disease diagnosis, medical treatment before and after MC treatment, dose of MC, mode of consumption, adverse effects of MC, employment status, impact of MC treatment on return to work (part-time or full-time work), and number of hours of work. Laboratory parameters included serological markers and vitamin  $B_{12}$  status.

In addition, all the patients completed the Revised Fibromyalgia Impact Questionnaire (FIQR) on the period before and after MC treatment.<sup>20</sup> The patients were asked to document any medical treatment they had received for fibromyalgia in the 2 months prior to starting MC treatment and during the 2 months while receiving MC treatment. Simple analgesics were considered paracetamol, dipyrone, or orphenadrine citrate combined with paracetamol. Mild opiates were considered tablets containing equal to or less than 30 mg of codeine or equal to or less than 100 mg tramadol per day. Strong opiates were considered any treatment containing oxycodone, patches containing fentanyl or buprenorphine, and tablets containing more than 200 mg tramadol per day. The participants were also asked about adverse effects associated with the use of MC. In the questionnaire, all the participants were asked to describe their experience of MC treatment in their own words.

For statistical analysis, Wilcoxon signed rank test was conducted to compare the results of questionnaire data before MC treatment with those after MC treatment. A  $\chi^2$  test was performed to compare the number of patients receiving different types of medications prior to MC treatment with the number of patients receiving the same types of medications while receiving MC treatment.

## **RESULTS**

Thirty patients were identified. One patient could not be contacted. Two patients had cancer, and 1 patient had inflammatory joint disease. Thus, 26 patients were included in the study. Nineteen patients ( $\sim$ 73%) were females, and the mean age of the study group was  $37.8 \pm 7.6$  years. The mean duration of a fibromyalgia diagnosis was  $4.3 \pm 2.64$  years. The mean dose of MC was  $26 \pm 8.3$  g per month, and the mean duration of treatment was  $10.4 \pm 11.3$  months, with a median duration of 3 months. No patient ceased MC treatment.

Table 1 summarizes the demographic and clinical parameters of the patients. All the patients smoked or inhaled MC. One of the 26 patients used a combination of smoking and oral oil drops. Table 2 summarizes the mean score for each item in the FIQR before and after MC treatment. Table 3 summarizes the various medications patients took in the 2 months prior to MC treatment and in the 2 months under MC treatment. In the study group, 13 patients (50%) ceased taking any medication other

TABLE 1. Demographics and Clinical Parameters of All the **Patients** 

Parameter	Results (%)
Sex, female:male	19:7
Age, <sup>a</sup> y	$37.8 \pm 7.6, 27-52$
Duration of fibromyalgia symptoms, a y	$7.6 \pm 6.3, 1-26$
Duration of fibromyalgia since diagnosis <sup>a</sup>	$4.21 \pm 2.59, 0.5-10$
Mean dose of MC, a g/mo	$26 \pm 8.3, 20-50$
Duration of MC treatment, a mo	$10.4 \pm 11.3, 1-42$
No. tender points <sup>a</sup>	$15.7 \pm 2.2, 12-18$
No. patients with headache	25 (~96)
No. patients with irritable bowel/bladder syndrome	9 (~35)
Pattern of MC use	
Smoked only	15 (~58)
Vaporized only	6 (~23)
Vaporized + smoked	3 (~14)
Oral drops + smoked	2 (~8)
<sup>a</sup> Mean ± SD, range.	

than MC. Twelve patients (~46%) reduced the dose/number of mediations by at least 50% as compared with the dose/ number of mediations prior to MC treatment. Table 4 summarizes the adverse effects of MC treatment reported by the patients.

## DISCUSSION

The main finding of the present study was that MC treatment was associated with significant favorable outcomes in every item evaluated in the FIQR. In some cases, the improvement was so marked that the patients completely ceased treatments they had taken previously. In other cases, the patients significantly reduced the dose or type of medication they had taken prior to MC treatment.

The patients expressed the effects of the treatment in their own words, and their responses were dramatic. Very rarely as physicians have we encountered such responses in real-life medicine, except possibly among patients treated with steroids for inflammatory conditions, such as polymyalgia rheumatica or rheumatoid arthritis.

Examples of the patients' responses were as follows: "I wish I had received this treatment when I was first diagnosed with fibromyalgia," "I returned to be the same person as before," "I regained my health," and "This is a miraculous treatment."

For some items of the FIQR, all the patients reported a favorable outcome. These included the effect of MC on pain and energy levels. For other items, the impact was less prominent, yet significant. These included the impact of MC on memory problems and daily activities of living, such as household activities (e.g., cleaning the house and changing bed sheets) and shopping (e.g., carrying grocery bags).

Another major benefit of MC treatment was a lack of serious adverse effects. The patients reported a few mild adverse effects, including dry mouth, redness of the eyes, and feeling hungry. These adverse effects appeared from the start of the treatment. The first 2 adverse effects were usually transient, lasting only a few weeks, and were mainly encountered in cases where the mode of MC was smoking. Many patients adapted to feeling hungry by eating prior to the use of MC.

The mean dose of MC consumed in the present study was relatively low (26  $\pm$  8.2 g per month) as compared with that

TABLE 2. FIQR Parameter Scores Prior to and Under MC Treatment

Parameter	Prior to MC Treatment <sup>a</sup>	Under MC Treatment <sup>a</sup>	P
Brush or comb your hair.	$7.12 \pm 3.18, 1-10$	$3.35 \pm 1.88, 0-6$	0.000
Walk continuously for 20 min.	$8.35 \pm 2.13, 3-10$	$3.51 \pm 1.97, 0-70$	0.000
Prepare a homemade meal.	$8.38 \pm 1.62, 5-10$	$4.13 \pm 2.34, 0-8$	0.000
Vacuum, scrub, or sweep floors	$9.51 \pm 1.21, 7 - 10$	$5.10 \pm 1.74, 2 - 8$	0.000
Lift and carry a bag full of groceries.	$8.52 \pm 1.68, 5 - 10$	$5.1 \pm 2.35, 2-9$	0.000
Climb 1 flight of stairs.	$7.88 \pm 1.83, 4 - 10$	$4.33 \pm 2.69, 0-9$	0.000
Change bed sheets.	$8.71 \pm 2.18, 3-10$	$5.04 \pm 2.79, 0 - 10$	0.000
Sit in a chair for 45 min.	$8.89 \pm 1.36, 6-10$	$4.05 \pm 2.61, 0 - 9$	0.000
Go shopping for groceries.	$8.67 \pm 1.42, 5 - 10$	$4.35 \pm 2.43, 0-9$	0.000
Fibromyalgia prevented me from accomplishing goals for the week.	$9.17 \pm 1.06, 7 - 10$	$3.77 \pm 1.87, 1-7$	0.000
I was completely overwhelmed by my fibromyalgia symptoms.	$9.39 \pm 0.94, 7 - 10$	$3.88 \pm 1.98, 1-7$	0.000
Please rate your level of pain.	$9.21 \pm 0.95, 7 - 10$	$3.35 \pm 1.64, 0-6$	0.000
Please rate your level of energy.	$9.37 \pm 0.79, 8-10$	$3.50 \pm 1.67, 1-7$	0.000
Please rate your level of stiffness.	$9.18 \pm 1.04, 7 - 10$	$4.27 \pm 1.7, 2-7$	0.000
Please rate the level of your sleep.	$9.23 \pm 1.59, 4 – 10$	$3.42 \pm 2.96, 0 - 10$	0.000
Please rate your level of depression.	$8.40 \pm 1.38, 5 - 10$	$2.77 \pm 2.11, 0-6$	0.000
Please rate your level of memory problems.	$6.96 \pm 2.73, 0-10$	$4.08 \pm 3.24, 0 - 10$	0.001
Please rat your level of anxiety.	$6.84 \pm 3.68, 0 - 10$	$2.42 \pm 2.37, 0-6$	0.000
Please rate your level of tenderness to touch.	$8.74 \pm 1.61, 5-10$	$4.1 \pm 2.76, 0-10$	0.000
Please rate your level of balance problems.	$6.95 \pm 2.81, 0-10$	$2.33 \pm 2.39, 0-8$	0.000
Please rate your level of sensitivity to loud noises, bright lights, odors, and cold.	$8.44 \pm 1.44, 6-10$	$3.82 \pm 2.46, 0 - 10$	0.000

<sup>&</sup>lt;sup>a</sup>Results are presented as mean ± SD, range.

consumed by patients who receive MC for other indications, such as cancer pain. In the latter case, the dosage exceeded 60 g per month (personal communication, Dr. Salem Billan, oncologist, Rambam Medical Center, Haifa, oral communication, on July 1, 2017). In the present study, many patients continued to take 30 or even 20 g per month, which were the lowest starting doses, suggesting that consumption of approximately 1 g or less a day could be sufficient to control most symptoms of fibromyalgia. The findings of the present study should reassure health policy makers and health care providers that most fibromyalgia patients will remain on a relatively low dose.

There are no studies on tolerance among MC users. However, a previous study of other recreational cannabis users found no tolerance to subjective effects of cannabis.<sup>21</sup>

In the current study, 12 patients (46%) reported either an improvement in their capacity to work or return to full-time work

TABLE 3. Meds Consumed Prior to and Under MC Treatment

	Prior to MC Treatment	Under MC Treatment	
Medication	No. Patients (%)	No. Patients (%)	P
Simple analgesics	12 (~46)	3 (~15)	0.000
NSAIDs	19 (~73)	2 (~8)	0.000
Simple opiates	4 (~15)	0 (0)	0.055
Pregabalin	7 (~27)	0 (0)	0.005
Strong opiates	20 (~77)	5 (~19)	0.000
Benzodiazepines	7 (~27)	1 (~5)	0.027
Tricyclics	4 (~15)	0	0.055
Other antidepressants	8 (~31)	3 (~12)	0.107

(data not shown). The aforementioned finding has implications for the patient, the patient's family, and society. A literature search revealed no studies on this issue of return to work, among patients treated with MC for different indications. However, a large study of the impact of illicit use of cannabis reported detrimental effects on employment and labor force.<sup>22</sup>

Although previous research proposed a role for endocannabinoid deficiency in fibromyalgia, <sup>23</sup> the potential role of endogenous cannabinoids in the pathogenesis of fibromyalgia remains unclear. More studies are needed to clarify their role. The distribution of cannabinoid receptors in the body may favor the proposed theory of central sensitization in the pathogenesis of fibromyalgia.

The long-term effects of MC treatment remain unclear. All MC request forms submitted to the Israeli Medical Cannabis Agency of the Ministry of Health that are signed by all patients clearly state that the long-term effects of MC are not known. Previous studies showed gray matter volume reductions in different parts of the cortex and functional impairments in various cognitive skills among cannabis users. <sup>24,25</sup> However, these studies involved individuals with heavy cannabis use and not patients under licensed MC treatment who received much lower doses.

Given the somewhat arbitrary selection of patients by the Israeli Medical Cannabis Agency to receive MC for their fibromyalgia, we do not know if the conclusions of our study could be generalized to all fibromyalgia patients, mainly those with severe pain. However,

**TABLE 4.** Adverse Effects of MC Treatment Reported by the Patients

Adverse Effect	No. Patients (%)	
Dry mouth	7 (~27)	
Red eyes	7 (~27)	
Hunger feeling	4 (~15)	

the consistent findings of the impact of MC on many of the FIQR items, especially on pain, allude to the validity of the results.

The main drawback of the present study was its retrospective nature, where patients were asked to answer questions regarding the period prior to their use of MC. However, most patients (~54%) answered the questionnaire a relatively short period after starting MC treatment (i.e., ≤3 months) Second, as mentioned earlier, fibromyalgia is not among the indications for MC treatment. Based on personal experience, fewer than 5% of requests for MC treatment for fibromyalgia are approved. Thus, it seemed unpractical to administer the questionnaire a priori to all patients with fibromyalgia whose doctor submitted a form for MC licensing.

### **REFERENCES**

- 1. Gostine M, Davis F, Roberts BA, et al. Clinical characterestics of fibromyalgia in a chronic pain syndrome [published online ahead of print April 18, 2017]. Pain Pract. 2017.
- 2. Arnold LM, Fan J, Russell IJ, et al. The fibromyalgia family study. A genome-wide linkage scan study. Arthritis Rheum. 2013;65:1122-1128.
- 3. Vincent A, Lahr BD, Wolfe F, et al. Prevalence of fibromyalgia: a population based study in Olmsted county, Minnesota, utilizing the Rochester epidemiology project. Arthritis Care Res (Hoboken). 2013;65: 786-792
- 4. Segura-Jiménez V, Álvarez-Gallardo IC, Carbonell-Baeza A, et al. Fibromyalgia has a larger impact on physical health then on psychological health, yet both are markedly affected: the Al-Ándalus project. Semin Arthritis Rheum. 2015;44:563-570.
- 5. MacLean AJ, Schwartz TL, Tramadol for the treatment of fibromyalgia. Expert Rev Neurother. 2015;15:469-475.
- 6. Derry S, Cording M, Wiffen PJ, et al. Pregabalin for pain in fibromyalgia in adults. Cochrane database Sys Rev. 2016;9:CD011790.
- 7. Kia S, Choy E. Update on treatment guideline in fibromyalgia syndrome with focus on pharmacology. Biomedicines. 2017;5.
- UNODC. World Drug Report 2015. Vienna, Austria: United Nations Office on Drugs and Crime; 2015.
- 9. Andre CM, Hausman JF, Guerriero G. Cannabis sativa: the plant of the thousand and one molecule. Front Plant Sci. 2016;7:19.
- 10. Piper BJ, DeKeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents of pain, anxiety, and sleep. J Psychopharmacol. 2017;35:569-575.
- 11. Mechoulam R, Mc Callum NK, Burstein S. Recent advances in the chemistry and biochemistry of cannabis. Chem Rev. 1976;76:75–112.

- 12. Mackie K. Cannabinoid receptors: where they are and what they do. J Neuroendocrinolo. 2008;(suppl 1):10-14.
- 13. Vogel Z, Barg J, Levy R, et al. A brain endogenous compound, interacts specifically with cannabinoid receptors and inhibits adenylate cyclase. J Neurochem. 1993;61:352-355.
- 14. Troutt WD, DiDonato MD. Medical cannabis in Arizona: patient characteristics, perceptions, and impressions of medical cannabis legalization. J Psychoactive Drugs. 2015;47:259-266.
- 15. Ko GD, Bober SL, Mindra S, et al. Medical cannabis-the Canadian perspective. J Pain Res. 2016;9:735-744.
- 16. Fiz J, Durán M, Capellà D, et al. Cannabis use in patients with fibromyalgia: effects on symptoms relief and health-Related quality of life. PLoS One. 2011:6:e18440.
- 17. Piper BJ, Beals ML, Abess AT, et al. Chronic pain patients' perspectives of medical cannabis. Pain. 2017;158:1373-1379.
- 18. Walitt B, Klose P, Fitzcharles MA, et al. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev. 2016;7:CD011694.
- 19. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010;62: 600-610.
- 20. Bennet RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther. 2009;11:R120.
- 21. Bedi G, Foltin RW, Gunderson EW, et al. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. Psychopharmacology (Berl). 2010;212:
- 22. Popovici I, French MT. Cannabis use, employment, and income: fixed-effects analysis of panel data. J Behav Health Serv Res. 2014;41:
- 23. Ethan BR. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. Cannabis Cannabinoid Res. 2016;1: 145-165.
- 24. Battistella G, Fornari E, Annoni JM, et al. Long-term effects of cannabis on brain structure. Neuropsychopharmacology. 2014;39: 2041-2048.
- 25. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med. 2011;5:1-8.