Adding medical cannabis to standard analgesic treatment for fibromyalgia: a prospective observational study

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ABSTRACT

Objective. *To assess any clinical improvement attributable to the addition of medical cannabis treatment (MCT) to the stable (≥3 months) standard analgesic treatment of fibromyalgia (FM) patients, the retention rate and any changes in the concomitant analgesic treatment over a period of six months.*

Methods. *The study involved 102 consecutive FM patients with VAS scores ≥4 despite standard analgesic treatment. Patients were prescribed two oil-diluted cannabis extracts: Bedrocan (22% THC, <1% CBD), and Bediol (6.3% THC, 8% CBD). FM severity was periodically assessed using Fibromyalgia Impact Questionnaire (FIQR), Fibromyalgia Assessment Scale (FAS), FACIT-Fatigue score, Pittsburgh Sleep Quality Index (PSQI), and Zung Depression and Anxiety Scales. During the study, patients were allowed to reduce or stop their concomitant analgesic therapy.*

Results. *The 6-month retention rate was 64%. A significant improvement in the PSQI and FIQR was observed in respectively 44% and 33% of patients. 50% showed a moderate improvement in the anxiety and depression scales. Multiple regression analysis showed a correlation between the body mass index (BMI) and FIQR improvement (p=0.017). Concomitant analgesic treatment was reduced or suspended in 47% of the patients. One-third experienced mild adverse events, which did not cause any significant treatment modifications.*

Conclusion. *This observational study shows that adjunctive MCT offers a possible clinical advantage in FM patients, especially in those with sleep dysfunctions. The clinical improvement inversely correlated with BMI. The retention rate and changes in concomitant analgesic therapy reflect MCT efficacy of the improved quality of life of patients. Further studies are needed to confirm these data, identify MCT-responsive sub-groups of FM patients, and establish the most appropriate posology and duration of the therapy.*

Introduction

Fibromyalgia syndrome (FM) is a poly-symptomatic disease characterised by chronic widespread pain, fatigue, sleep disturbances and cognitive symptoms (1-2). Its mean population prevalence of 2.7% worldwide (3) and 4.7% in Europe (4) makes it the third most prevalent rheumatic disease after lumbar pain and osteoarthritis (5). However, its largely unknown pathogenesis makes it extremely difficult to find a satisfactory medical treatment, and the limited efficacy and side effects of first-line pharmacotherapies leads to poor patient compliance. There is therefore a need for more efficacious combination approaches (6).

Medical cannabis treatment (MCT) is a recently introduced therapeutic option for patients who are dissatisfied with their current analgesic therapy, and has proved to be moderately effective in a number of chronic non-cancer pain conditions (7-8). It has been hypothesised that FM is a "clinical endocannabinoid deficiency disease" (9), although the role of the cannabinoid system in FM is still unclear and the effectiveness of MCT has been investigated in only a few studies involving FM patients. One very recent trial (10) has compared the effectiveness of a single vapour inhalation of three cannabis preparations (Bedrocan, Bediol and Bedrolite), and found that those containing THC significantly increased the pressure pain threshold in comparison with placebo; another recent observational study (11) has shown that the addition of MCT to oxycodone and duloxetine is efficacious in treating lumbar pain in FM patients; and an Israeli retrospec-

tive study (12) has found that MCT leads to significant improvements in many Fibromyalgia Impact Questionnaire (FIQ) parameters, thus suggesting its potential therapeutic role.

The aim of this prospective observational study was to investigate the efficacy and side effects of MCT as part of a multi-drug regimen for FM patients who had received stable analgesic therapy for >3 months but still had a pain visual analogue scale (VAS) score of ≥4. Validated clinimetric tests were used to assess clinical improvement in terms of subjective pain relief, fatigue, sleep, anxiety, depression, other FM-related symptoms, and the quality of life. We also investigated the treatment retention rate, the reasons for any treatment discontinuations, and the changes in concomitant analgesic treatment over a period of six months.

Table I. Baseline analgesic treatment. Most of the patients were taking two or more drugs.

Active principle	n. of treated patients	Posology
Pregabalin	37/66	25-300 mg
Duloxetine	35/66	30-60 mg
Gabapentin	15/66	300-1800 mg
Cyclobenzaprine	15/66	10-20 mg
Tapentadol	10/66	50-200 mg
Tramadol	12/66	50-200 mg
Venlafaxine	5/66	37.5-150 mg
1 drug	15/66	
2 concomitant drugs	31/66	
≥3 concomitant drugs	20/66	

Methods

Ethical considerations

The protocol of this single-centre, prospective observational study (Fibrocan), which was carried out at the Rheumatology Unit of Luigi Sacco University Hospital in Milan, Italy, was approved by the local Institutional Review Board. All the patients gave their written informed consent before enrolment.

Participants

The study involved 102 consecutive FM patients not responding to standard analgesic treatment. The inclusion criteria were a pain VAS score of ≥4 persisting for most of the day (a verbal pain scale ranging from 0 = no pain to 10 = worst pain imaginable) and satisfying the 2010 American College of Rheumatology (ACR) diagnostic criteria for FM (a widespread pain index [WPI] of ≥7 on a scale ranging from 0 to 19, and a symptom severity score [SSS] of ≥5 on a scale ranging from 0 to 12, or a WPI of 3-6 and an SSS of ≥9). The exclusion criteria were an age of <18 years; any rheumatological, neurological or psychiatric illness; any known allergies to the study medication; illicit drug or alcohol use; recent cannabis use; pregnancy; breastfeeding; and the presence of a pain syndrome other than FM.

Table I shows the standard analgesic treatments that the 66 patients completing the study had been receiving for at least three months before entering the study. Any additional personalised non-pharmacological treatment was allowed and, during the study, the patients could reduce or stop their concomitant analgesic therapy.

Study design

Medical cannabis consists of the dried, pulverised and homogenised flowers of *Cannabis sativa L.* cultivated under standardised conditions in accordance with the requirements of good manufacturing practices. Two distinct pharmaceutical-grade cannabis preparations were used, both of which were obtained from Bedrocan International BV (Veendam, The Netherlands) and prepared by Proxy Laboratories BV (Leiden, The Netherlands): Bedrocan, which contains 22% tetrahydrocannabinol (THC) (220 mg/g) and less than 1% cannabidiol (CBD), and Bediol, which contains 6.3% THC (63 mg/g) and 8% CBD (80 mg/g). The patients obtained the medical cannabis by submitting a prescription specifying the THC and CBD content. The full cannabis plant extract was prepared in specialised pharmacies starting from standardised cannabis plant material (cannabis flos) by means of Romano-Hazekamp or Sifap-Sifo extraction, and diluted in oil (1 g of cannabis in 10 g of olive oil).

The patients visited our outpatient clinic for their initial drug prescriptions and subsequent follow-up examinations. On their first visit, they were instructed how to take the drug and informed about its possible side effects. Treatment was started slowly, beginning with a low night-time dose of Bedrocan followed by Bediol in the morning. Dose prescribed ranged from 10 to 30 drops of pharmaceutical, trying to maintain the same dosage for both formulations. As the ideal MCT dosing schedule is currently unknown (no dose-finding studies have yet examined the optimal daily amount of specific molecular concentrations of THC and CBD), subsequent individualised dose escalations were allowed but were not to exceed a total of 120 drops per day. The first follow-up visit was 4–8 weeks after starting MCT; the subsequent visits were scheduled every 2–3 months. During each visit, questionnaires were used to assess efficacy and side effects.

Outcome measures

The outcome measures were dimension-specific, symptom-specific and disease-specific clinimetric measurements of widespread pain, fatigue, sleep disturbances, mood, overall well-being, and the components of health status that are believed to be the most affected by FM (13).

The Italian version of the Revised Fibromyalgia Impact Questionnaire (FIQR) (14) is a disease-specific instrument consisting of 21 items concerning the previous seven days that are rated by means of a 0-10 numeric rating scale in which 10 is "the worst". It is divided into three linked domains: 1) physical function (nine items); 2) the overall impact of FM on functioning and overall symptom severity (two questions); and 3) symptoms (ten questions), including memory, tenderness, balance, and environmental sensitivity to loud noises, bright lights, odours and cold tem-

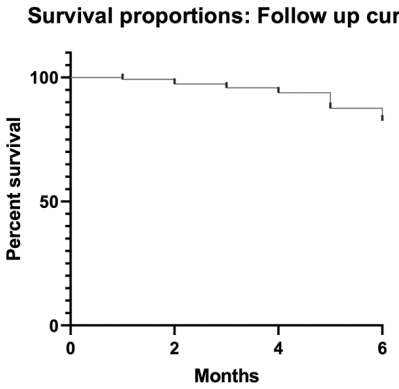

Fig. 1. Six-month Kaplan-Meier curve of study survival.

Table II. Demographic data and baseline clinical characteristics of the 66 patients completing the study.

Age (SD), years	51.9 (11.3)
Females	91%
Males	9%
Weight (SD), kg	68.7 (14.3)
Height (SD), m	1.65 (0.08)
BMI (SD), kg/m^2	25.16 (4.97)
Disease duration (SD), months	114.3 (81.5)
WPI	12.3 (4.7)
SS1	7 (1.8)
SS2a	2.2 (0.8)
SS2b	1.9 (0.6)

BMI: body mass index; SD: standard deviation; SSS: symptom severity score; WPI: widespread pain index.

peratures. The total "physical function" score (range 0-90) is divided by three, the total "overall impact" score (range 0-20) remains unchanged, and the total "symptom" score (range 0-100) is divided by two: the total FIQR score is the sum of the three adjusted scores.

The Fibromyalgia Assessment Status (FAS) is a validated disease-specific composite measure for patients with FM (15) that combines scores relating to fatigue (range 0–10) and the quality of sleep (range 0–10) with Self-Administered Pain Scale (SAPS) scores in order to provide a single measure of disease activity (range 0–10). The SAPS requires patients to classify pain in 16 non-articular sites on a scale ranging from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe), and the final total score of 0-48 is normalised to a scale of 0–10.

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale is widely used to assess cancer-related fatigue. Its 13 items are rated using a 5-point scale (from 0 = not at all to 4 = very much), and the total score is the sum of the individual items, which ranges from 0 (maximum fatigue) to 52 (no fatigue).

The Pittsburgh Sleep Quality Index (PSQI) retrospectively measures sleep quality and disturbances, and provides a brief but clinically useful assessment of multiple sleep disturbances. It consists of 19 items that generate seven component scores, the sum of which (range 0–21) yields a global measure of sleep quality, with higher scores indicating poorer sleep (>5 indicates sleep disturbance).

The Zung Self-Rating Depression Scale (ZSR-D) is a 20-item instrument that quantifies depression on the basis of 10 positively and 10 negatively worded questions concerning depressive symptoms. Each question is scored on a scale of 1-4 (1 = little or none of the time, 2 = some of the time, 3 = a large part of the time, 4 = most of the time). The total score is the sum of the individual responses, with higher scores indicating more significant depression.

The Zung Self-Rating Anxiety Scale (ZSR-A) is a 20-item instrument that quantifies anxiety on the basis of questions concerning four groups of anxiety manifestations: cognitive, autonomic, motor and central nervous system symptoms. Each question is scored on a scale of 1-4 (1 = little or none of the time, 2 = some of the time, 3 = a large part of the time, 4 = most of the time). The total score is the sum of individual responses, with higher scores indicating more significant anxiety.

Table III. Baseline, and 3- and 6-month mean and median values, standard deviations and 95% confidence intervals of the FAS scores of the patients who continued MCT for at least six months.

	Mean	Median	SD	25-75 *p*
BASELINE				
FAS Fatigue	8.379	9	2.146	8.000-10.000
FAS Pain	6.392	6.7	2.137	4.600-8.000
FAS Sleep	8.288	9	2.479	7.000-10.000
FAS Total	7.698	8.3	1.939	7.125-9.100
3 MONTHS				
FAS Fatigue	7.348	8	2.551	6.000-10.000
FAS Pain	5.771	5.9	2.277	4.000-7.700
FAS Sleep	7.015	8	2.697	5.000-10.000
FAS Total	6.710	7	2.097	5.775-8.248
6 MONTHS				
FAS Fatigue	7.727	8	2.421	6.000-10.000
FAS Pain	6.098	6.25	2.208	4.400-7.700
FAS Sleep	7.470	8	2.488	6.000-10.000
FAS Total	7.030	7.4	2.100	5.900-8.500

MCT: medical cannabis therapy; FAS: Fibromyalgia Assessment Scale; SD: standard deviation.

Statistical analysis

Descriptive statistics were used to summarise the clinimetric scores collected over time. The continuous data are presented as mean values and standard deviations, and the categorical data as proportions. The patients lost to follow-up and those who stopped the study treatment for reasons deemed to be unrelated to the drug were right censored. The time to discontinuation was defined as the time between the first and last drug administration. Crude drug retention rates and mean survival times were estimated using the Kaplan-Meier life-table method. The estimated hazard ratios of discontinuing treatment were assessed by means of a multivariate Cox regression model with the stepwise backward selection of the covariates of age, BMI, disease duration, PSQI, sex, WPI, ZSR-A and ZRS-D. Cox regression models with backward selection were constructed for each parameter in order to estimate the baseline predictors of clinical outcomes.

Table IV. Baseline, and 3- and 6-month mean and median values, standard deviations and 95% confidence intervals of the FACIT, PSQI, ZSR-A and ZSR-D scores of the patients who continued MCT for at least six months.

	Mean	Median	SD	25 – 75 P
BASELINE				
FACIT	18.379	18	9.939	12.000-22.000
PSQI	10.554	11	3.206	9.000-13.000
ZSR-A	64.754	68	12.585	55.750-73.000
ZSR-D	52.758	53	10.728	47.000-60.000
3 MONTHS				
FACIT	22.848	20	11.633	16.000-30.000
PSQI	9.061	9	3.423	7.000-12.000
ZSR-A	61.288	61	13.081	54.000-70.000
ZSR-D	50.152	51.5	11.151	42.000-57.000
6 MONTHS				
FACIT	21.288	20	11.558	14.000-28.000
PSQI	9.001	9	3.641	7.000-12.000
ZSR-A	61.924	63	13.193	54.000-71.000
ZSR-D	50.815	50	11.777	43.000-58.500

MCT: medical cannabis therapy; FACIT: Functional Assessment of Chronic Illness Therapy; FAS: Fibromyalgia Assessment Scale; PSQI: Pittsburgh Sleep Quality Index; SD: standard deviation; ZSR-D: Zung Self-rating Depression scale; ZSR-A: Zung Self-rating Anxiety scale.

Table V. Baseline, and 3- and 6-month mean and median values, standard deviations and 95% confidence intervals of the FIQR scores of the patients who continued MCT for at least six months.

	Mean	Median	SD	25 - 75 P
BASELINE				
FIQR General Status	13.545	16	5.878	9.000-18.000
FIQR Physical	20.109	21.3	6.132	16.000-24.300
FIQR Symptoms	35.417	37.5	9.229	30.000-42.500
FIQR Total	69.003	72.75	19.181	54.800-84.500
3 MONTHS				
FIQR General Status	11.409	12	6.201	6.000-16.000
FIQR Physical	17.821	19.15	7.322	12.300-23.000
FIQR Symptoms	31.076	31.75	11.211	23.500-40.000
FIQR Total	60.585	65	23.393	44.000-79.000
6 MONTHS				
FIQR General Status	12.258	12	5.938	8.000-17.000
FIQR Physical	18.624	19.60	7.403	16.000-23.600
FIQR Symptoms	31.432	31.25	10.655	25.500-40.000
FIQR Total	62.252	64.80	22.751	50.600-79.600

MCT: medical cannabis therapy; FIQR: Fibromyalgia Impact Questionnaire Revised; SD: standard deviation.

Results

The study was completed by 66 of the originally recruited 102 consecutive FM patients: 25 patients (24.5%) were lost to follow-up (10 of whom continued MCT at another centre), and 11 (10.7%) voluntarily discontinued the study treatment (three because of a lack of clinical benefit; six because of adverse events, mainly nausea, palpitations and dizziness; and two because of the high cost of the treatment) (Fig. 1). Table II shows the demographic data and baseline characteristics of the 66 patients who completed the study. It is worth noting that 40.9% of the patients were moderately overweight (BMI ≥25 kg/m^2) and 13.6% were obese (BMI ≥30 kg/m^2).

Tables III-V show the results of the clinimetric tests at baseline and after three and six months of MCT.

The patients were divided into outcome groups on the basis of the percentage changes in each clinical parameter between the start of the study (baseline) and the end of six months of treatment. On the basis of previously published data, a decrease of ≥30% was considered a significant clinical improvement; a decrease of 10-29% a moderate clinical improvement; a decrease or increase of 10% a stable clinical situation; an increase of 10-29% moderate clinical worsening; and an increase of ≥30% significant clinical worsening.

Figures 2-4 show the number of patients falling into each outcome group for each clinimetric test. It can be seen that there were significant differences between the measures: there was almost no improvement in the FAS scores, with 45.5% of the patients remaining in a stable clinical condition; the FACIT-Fatigue scores showed that 54.5% of the patients experienced significant clinical worsening; the PSQI and FIQR scores showed a significant clinical improvement in respectively 44% and 33% of the patients; and the ZRS-A and ZRS-D scores showed a moderate improvement in respectively 42.4% and 50%.

Furthermore, multiple regression analysis showed that the BMI played a significant role (p=0.017) as it was the only covariate explaining an improvement of at least 30% in the FIQR (Table V).

During the study, 31 of the 66 patients (47%) reduced (17 patients) or discontinued (14 patients) their concomitant analgesic treatment (Fig. 5), something that reflects their perception of the efficacy of MCT and the improvement in their quality of life.

One-third of the patients completing the study experienced adverse events, which were mild to moderate in severity and did not cause any significant treatment modifications. Figure 6 shows the relative frequency of each reported adverse event, the most frequent of which were dizziness (21%), sleepiness (16%), palpitations (12%), nausea (9%) and xerostomia (9%). There were no serious adverse events.

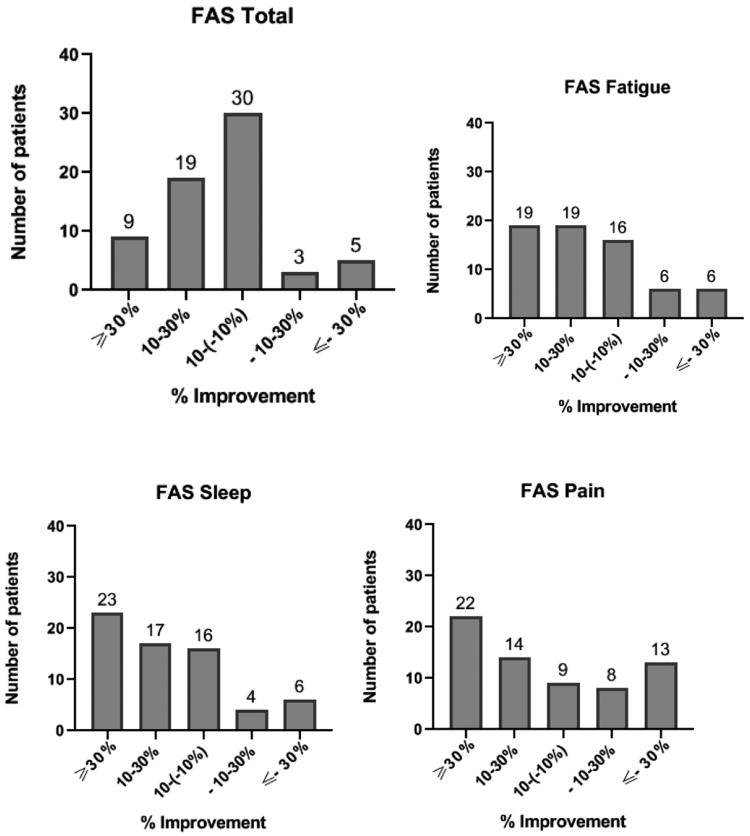

Fig. 2. The number of patients in each FAS outcome group. A ≥30% improvement was considered significant.

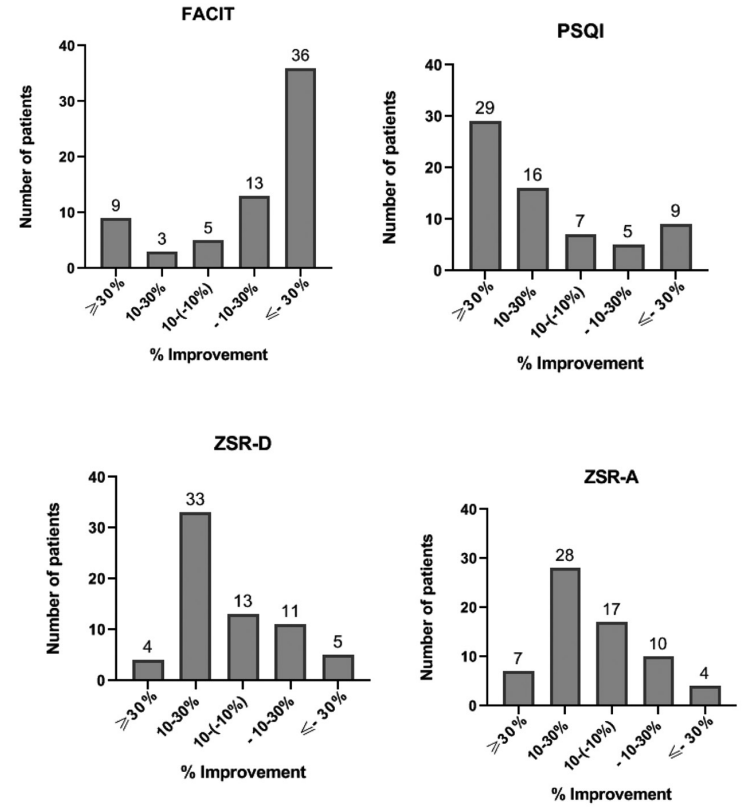

Fig. 3. The number of patients in the FACIT, PSQI, ZSR-A and ZSR-D outcome groups. A ≥30% improvement was considered significant.

Discussion

The findings of this observational study show the substantial clinical advantage of using MCT in addition to standard chronic (>3 months) analgesic treatment in a group of typical FM patients: >30% of the patients achieved a ≥30% clinical improvement in their PSQI (sleep dysfunction decreases the patients' quality of life and correlates with pain severity) (16-17) and FIQR scores. A considerable proportion of patients also achieved albeit smaller improvements in ZRS-A and ZRS-D. Significant psychological distress is very common in FM patients (it is estimated that up to 80% patients meet the criteria for depression and/or anxiety depending on the clinical setting) (18), and may evolve into a full-blown psychiatric disorder. Adjunctive MCT may therefore be considered, especially in the FM sub-population suffering from significant sleep disturbances and mild anxio-depressive symptoms.

FM patients are not homogenous, but should be divided into sub-groups on the basis of their main clinical symptoms and treated accordingly. Our analysis shows that BMI is the covariate that most closely correlates with an improvement in FIQR scores, a correlation that may be related to cannabinoid liposolubility: patients with a higher BMI need higher doses because of the drug's pharmacokinetics (19). Furthermore, it is known that BMI influences peripheral and neuroinflammation (20), and this play a significant role in the pathogenesis and maintenance of FM, which has both centrally and peripherally mediated mechanisms of pain amplification (21-23).

MCT has proved to be a much safer adjunct than opioid treatment, which is associated with a high risk/benefit ratio and is not effective in treating FM (24); furthermore, MCT does not have any substantial addictive properties in terms of dose escalation or withdrawal syndrome (25-26). The most significant concern is tolerance because, although symptom relief is obtained after only three months, a longer treatment period could lead to declining effectiveness, although this can be avoided by extremely slow dose titration.

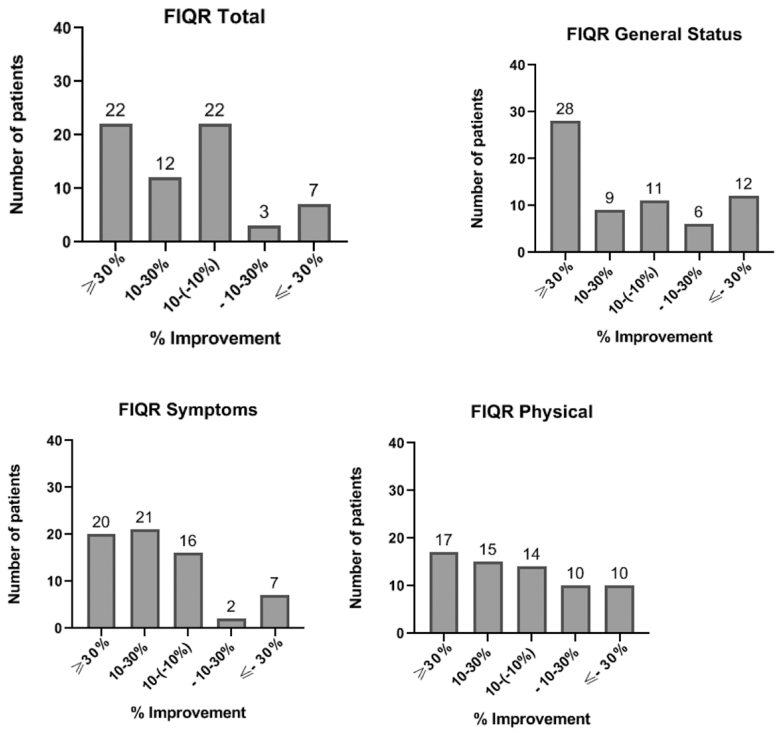

Fig. 4. The number of patients in each FIQR outcome group. A ≥30% improvement was considered significant.

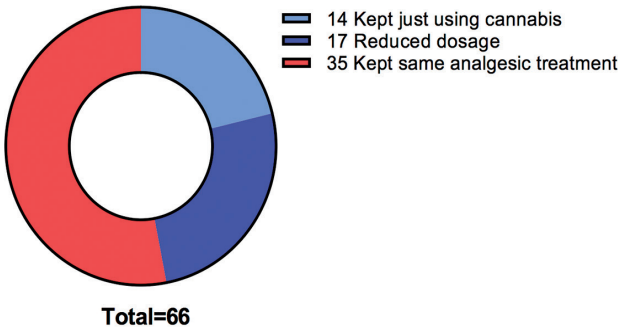

Fig. 5. Changes in the concomitant analgesic treatment of the patients completing the study.

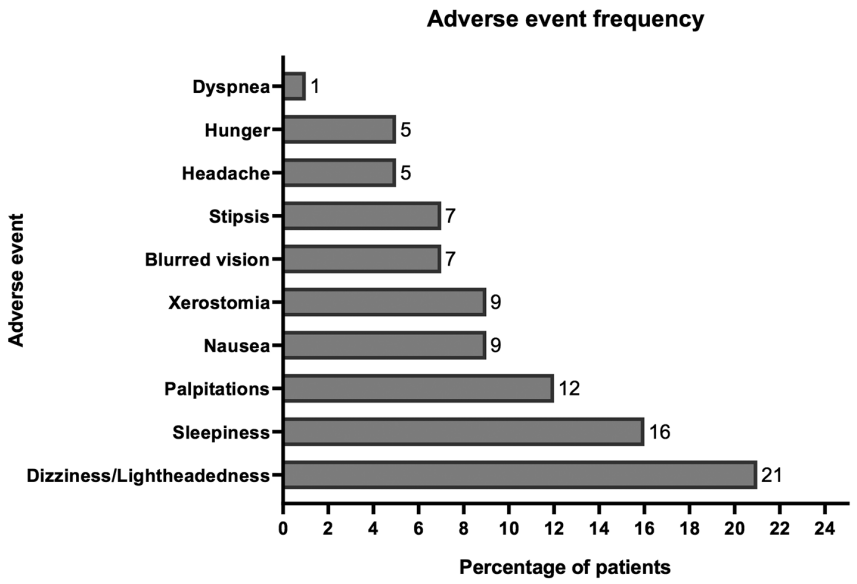

Fig. 6. Incidence of the MCT-related adverse events reported after three and six months of treatment.

We found that the MCT retention rate was quite high in comparison with the usually poor treatment compliance of FM patients in general (27). The 6-month retention rate was 64%, and only 6% of the patients discontinued the treatment because of adverse events: it is also worth noting that ten of the 25 patients who were lost to follow-up continued MCT at another centre. Furthermore, after the six-month study period, 14 patients continued using MCT alone and 17 reduced the dose of their concomitant analgesic therapy: this probably reflects their subjective satisfaction with the efficacy and side effects of MCT, although further studies are needed to confirm this hypothesis.

This is one of the first studies investigating the role of MCT in FM. Most studies used nabilone, a purely synthetic cannabinoid (28-29), which is completely different from whole cannabis flowers: they have a complex and not fully understood mechanism of action that depends on their different THC/CBD ratios and their synergism with other components (30). It is therefore important to try various cannabis preparations in treating the same disease. This rationale lies behind the use of two different formulations in the present study: a higher THC/CBD ratio has more potent analgesic properties (10), but cannot be used in the morning for legislative concerns. On the other hand, a lower THC/CBD formulation can be taken in the morning since it is associated with less drowsiness. It is clear that in general, since an ideal MCT formulation and dose is still under investigation for FM, the treatment strategy is empirical and based on clinical experience. Other major strengths of this study include the relatively large number of completers (66), the long treatment period (6 months), and the fact that MCT was administered orally rather than by means of inhalation (which is particularly useful in the case of chronic conditions) (19-31). Finally, we used many disease-specific clinimetric parameters that have been validated for FM.

The limitations of the study are that its observational design does not allow a comparison with a control group, and the fact that the patients were treated

with two preparations that have different THC/CBD ratios, thus making it difficult to differentiate the effects of each active principle.

In conclusion, these findings of this study, conducted in response to the need to find new drugs for FM patients whose standard therapy is insufficiently effective, showed that MCT offers a clinical advantage in terms of efficacy, especially for its effects on sleep and quality of life. However, further studies are required to establish the best therapeutic strategy in terms of posology, the THC/CBD ratio, and treatment duration. It is also important to determine the subgroups of FM patients whose symptoms are most responsive to treatment.

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