The effect of medical cannabis on gastrointestinal symptoms in fibromyalgia and disorders of gut-brain interaction: a patient-centred real-world observational study

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Abstract

Objective

Fibromyalgia (FM) is frequently associated with gastrointestinal (GI) disorders such as disorders of gut-brain interaction (DGBIs). Current treatments for FM offer limited relief, leading to the exploration of alternative therapies such as medical cannabis. This study evaluates in the impact of Bedrocan® medical cannabis in FM patients and GI symptoms over six months.

Methods

Sixty FM patients were enrolled, receiving a Bedrocan® cannabis treatment for 6 months. A standardised questionnaire evaluating upper and lower GI symptoms and the Revised Fibromyalgia Impact Questionnaire (FIQR) evaluating FM severity were administered at enrolment and 3 and 6-month follow-up evaluations. DGBIs, in particular, irritable bowel syndrome (IBS), and functional dyspepsia (FD) were diagnosed according to Rome IV criteria.

Results

Forty-six/60 (76.6%) FM patients fulfilled the diagnostic criteria for at least one DGBI; 10/60 (16.7%) FM patients fulfilled the diagnostic criteria for IBS, 17/60 (28.3%) for FD, and 19/60 (31.7%) for both IBS/FD. The FIQR severity score log-transformed significantly decreased during the months-by-month comparison period (repeated-measures ANOVA, $p<0.001$). Among GI symptoms, the log-transformed intensity-frequency score of epigastric pain, epigastric burning, abdominal pain, abdominal distension, and bloating significantly decreased during the month-by-month comparison period (repeated-measures ANOVA, $p<0.01$).

Conclusion

This study supports Bedrocan® medical cannabis as an alternative treatment for FM with a potential effect on FD and IBS symptoms. Despite positive outcomes, the study acknowledges limitations, such as the small sample size and absence of a control group. Further research is required to confirm the efficacy of medical cannabis in FM patients, particularly regarding its effects on GI symptoms.

Key words

fibromyalgia, medical cannabis, gastrointestinal symptoms, irritable bowel syndrome, functional dyspepsia

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Introduction

Fibromyalgia (FM) is a chronic, debilitating condition, characterised by the presence of widespread pain, in the absence of peripheral abnormalities or tissue inflammation (1). It is defined as a central sensitisation syndrome, in which the altered perception, transmission, and processing of nociceptive stimuli play a fundamental role (2, 3).

The FM worldwide prevalence is about 2-4% (4), and women are more frequently affected than men. FM can occur alone but is often associated with sleep disturbances, chronic fatigue, psychiatric comorbidities (*i.e.*, depression, anxiety and personality disorders), migraine and temporal mandibular disorders (1, 5, 6). FM negatively affects patients' quality of life and work productivity (7).

The disorders of gut-brain interaction (DGBIs) are complex, multifactorial conditions characterised by chronic or recurring gastrointestinal (GI) symptoms in the absence of any structural or biochemical abnormalities (8, 9). DGBI diagnosis relies on Rome-IV criteria, that describe 33 distinct adult DGBIs including irritable bowel syndrome (IBS), and functional dyspepsia (FD).

Several previous studies have described the high prevalence of FM in patients with IBS (ranging from 28 to 65 %) and, vice versa (32-80%) (10-12). However, only a few data are available about the association of FD and FM (13-15). A recent study demonstrated that 49% of FM patients fulfilled the diagnostic criteria for IBS, and 81.6% for FD, with an overlap for both IBS/FD in 44.9% of patients according to Rome IV criteria. Moreover, there was a graduated increase in the severity of symptoms when FM and DGBI coexisted (16).

Treatments currently indicated for FM include antidepressant and pain-relieving medications, cognitive behavioural therapy (CBT), and exercise therapy (17, 18). However, the effectiveness of these therapeutic approaches remains rather limited, and other treatments have been explored. Previous studies evaluated the efficacy of medical cannabis (MC) sativa in FM patients, increasing evidence that suggest that the endocannabinoid (eCB) system, a complex pleiotropic signalling system, might be a potential target for an effective therapeutic strategy in FM. In particular, the two most studied components of MC were the phytocannabinoids delta-9-tetrahydrocannabinol (THC) and the cannabidiol (CBD) that act on type 1 (CB1) and type 2 (CB2) cannabinoid receptors with a different affinity. Indeed, THC, the main psychoactive component of MC, acts as a partial CB1 receptor agonist, inducing analgesia through inhibition of pain-activated neurons. It also appears to act positively on mood and appetite (16). CBD, on the other hand, behaves as a low-potency inverse agonist/antagonist on both CB1 and CB2 receptors through a noncompetitive mechanism. CBD, in addition to its intrinsic analgesic and anti-inflammatory properties, binds to multiple pain-associated proteins to desensitise them and achieve analgesia (17). It also potentiates the psychoactive and nonpsychoactive effects of THC, such as anxiety, sedation, and tachycardia.

Therefore, the balanced combination of THC and CBD could have a synergistic analgesic effect of both components (19).

A recent systematic review suggests that medical cannabis might be a safe alternative for treating pain in FM patients. However, the high disparity and inconsistency in the methodology of the available studies precludes drawing any strong conclusions about its efficacy (19).

The eCB's role was also considered in the pathogenesis of IBS, and a clinical endocannabinoid deficiency was proposed as a pathophysiological mechanism underlying many of the IBS manifestations (20, 21). Furthermore, studies on animal models suggested the relevant role of cannabinoids on several pathogenetic mechanisms of DGBI such as the epithelial tight junctions, mast cell and macrophage activation in the mucosa, and the interaction between the gut microbiota and the immune system. However, convincing evidence of efficacy is still lacking in humans (22).

This study aims to evaluate the changes in the severity of FM symptoms and of the upper GI (epigastric pain, epigastric burning, postprandial fullness, early satiety) and lower GI (abdominal pain, abdominal distension, bloating) symptoms, after treatment with MC.

Methods

Population

We prospectively recruited 60 consecutive FM outpatients, followed at the Division of Immunology and Rheumatology of the University Hospital "San Giovanni di Dio e Ruggi d'Aragona" of Salerno. FM was diagnosed according to the 2016 revised criteria of the American College of Rheumatology (ACR) (23). At enrolment, demographic characteristics (gender, age, and smoking habits), anthropometric data (weight, height, and BMI), and prevalence of comorbidities, *i.e.*, hypertension, dyslipidaemia, type 2 diabetes mellitus, and thyroid diseases, were collected. The type of medications used was also recorded. Stool consistency was recorded using the Bristol Stool Form Scale (BSFS), as a numerical value. The number of daily bowel movements was expressed as mean, weekly. FD and IBS were diagnosed by two experienced gastroenterologists in the field of DGBI according to Rome IV criteria (9) in all patients, together with excluding any organic disease, with a complete physical examination, blood tests, and additional tests when indicated. Four different patterns of IBS resulted from the predominant bowel symptom: (a) diarrhoea-predominant (IBS-D); (b) constipation-predominant (IBS-C); (c) mixed IBS (IBS-M); and (d) undetermined IBS (IBS-U). The two considered FD subgroups were the postprandial distress syndrome (PDS) and the epigastric pain syndrome (EPS). Inclusion criteria were as follows: Caucasian adults aged from 18 to 60 years; diagnosis of FM non-responder to traditional therapy (pregabalin, duloxetine, cyclobenzaprine, tramadol). Exclusion criteria were pregnancy, alcohol abuse, and any organic GI diseases. All the enrolled patients started the therapy with Bedrocan® medical cannabis with a THC level standardised at 19% and with a CBD level below 1%. The cannabis dose for each patient was determined according to the pain level evaluated by an expert rheumatologist (P.M.). The dose is usually administered orally as a rapidly dissolving solution, and all patients were instructed to gradually increase the dosage (1 drop/day) up to a maximum of 20 drops/day (equivalent to approximately 20 mg of cannabis) until they achieved a therapeutic effect (*e.g.*, subjective pain relief or significant improvement in quality of life). Moreover, in case of adverse events, patients were instructed to use the last dosage that did not cause undesirable symptoms. All the patients were naïve to cannabis treatment.

This study was approved by "ASL Napoli 3 Sud" Research Ethics Committee (approval no. 0089264) on June 13, 2019. Informed consent, for participation and publication, was obtained from every enrolled patient.

Questionnaires

All patients underwent the following validated questionnaires before starting the therapy and after 3 and 6 months.

– *Standardised GI symptoms questionnaire*. A previously published standardised questionnaire (24) dealing with the presence, the frequency from 0 to 3 (0 absent, 1=≤2 d/wk; 2=3–5 d/wk; and 3=≥6 d/wk), and the intensity from 0 to 3 (0=absent; 1 not very bothersome, not interfering with daily activities; 2=bothersome, but not interfering with daily activities; and 3=interfering with daily activities), of both upper and lower GI symptoms, was used in all patients. For each symptom, a frequency-intensity score from 0 up to a maximum of 6 was obtained. GI symptom scores were also categorised into three groups (absent=0, mild=from 1 to 3, severe=from 4 to 6).
– *The Revised Fibromyalgia Impact Questionnaire (FIQR*) is a self-administered, validated questionnaire, that consists of 21 items. Each item is based on an 11-point numeric rating scale of 0 to 10, with 10 being 'worst'. All questions are framed in the context of the past 7 days. The FIQR is designed to evaluate three main domains: physical function (9 items), overall impact (2 items), and FM symptoms (10 items). The total score is calculated as the algebraic sum of the three domain scores, and it ranges between 0 and 100. Higher scores indicate more severe disease. An Italian multicentre study (25) suggested cut-off values for the FIQR total score: ≤23 remission, >23 and ≤40 mild disease activity, >40 and ≤63 low disease activity, >63 and ≤82 severe disease activity and >82 very severe disease activity.

Follow-up

FM patients were evaluated after 3 (T1 evaluation) and 6 months (T2 evaluation) from the beginning of therapy. At each follow-up visit, GI symptoms were investigated using the standardised questionnaire, and side effects of medical cannabis therapy were collected. Moreover, patients filled in the FIQR questionnaire.

Statistical analysis

Frequencies, means and standard deviations (SD) for discrete or continuous variables were computed, respectively. When appropriate, a χ^2 test was calculated to compare categorical data. Spearman' and Pearson's correlations were used as appropriate.

In this study, the analyses for the primary endpoints were the changes in the severity of FM symptoms, and of the GI upper (epigastric pain, epigastric burning, postprandial fullness, early satiety) and lower (abdominal pain, abdominal distension, bloating, mean weekly number of evacuations and Bristol stool scale form) symptoms, at 0, 3- and 6-months of treatment with MC, using a repeated measures ANOVA model. When nonparametric, the scores were log-transformed to be more easily used. FM remission was defined as a FIQR score less than 23 and calculated according to the intention-to-treat principle, i.e. all enrolled patients were included in the analysis and per-protocol analysis, i.e. patients who completed the T1 and T2 evaluations.

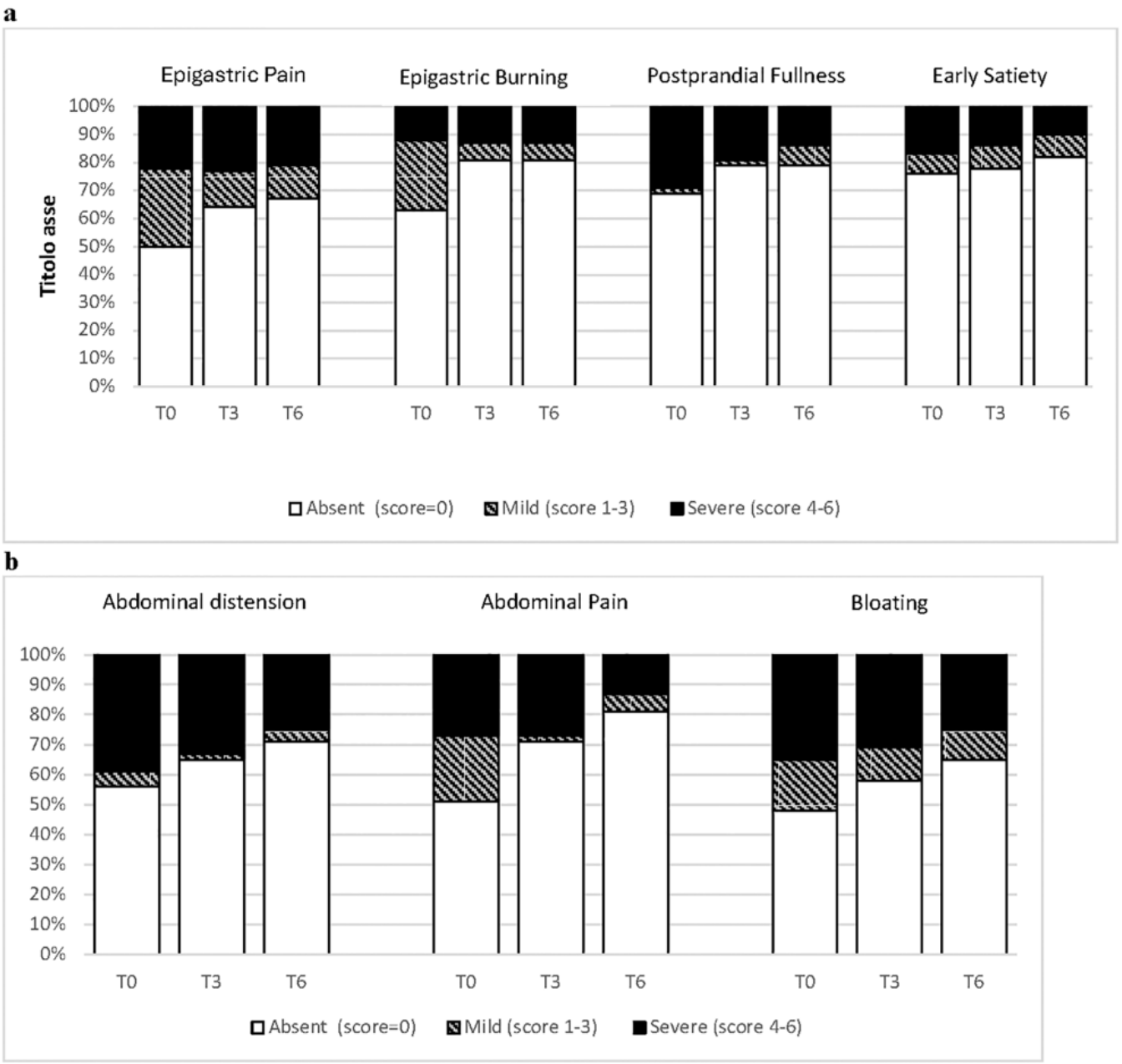

Fig.1. Upper (epigastric pain, epigastric burning, postprandial fullness, early satiety) (**a**) and lower GI (abdominal pain, abdominal distension, and bloating) symptom scores (**b**) categorised as absent, mild, and strong, evaluated at baseline (T0), 3 months after therapy with MC (T1), and 6 months after therapy with medical cannabis (T2).

Significance was expressed at $p<0.05$ level. SPSS for Windows (release 15.0; SPSS Inc. Chicago, IL, USA) was used for statistical analysis.

Results

Baseline evaluation (T0)

60 FM patients (58 women, 96.6%) were enrolled. The mean age was 58±11.4 years; the mean BMI was 28.2±5.6 Kg/m^2. Eight/60 (13.3%) of FM patients were affected by hypertension, 2/60 (3.3%) by dyslipidaemia, 3/60 (5%) by type 2 diabetes mellitus, and 6/60 (11.7%) by thyroid diseases.

Forty-six/60 (76.6%) FM patients fulfilled the Rome IV diagnostic criteria for at least one DGBI. In particular, 10/60 (16.7%) FM patients fulfilled the diagnostic criteria for IBS, 17/60 (28.3%) for FD, and 19/60 (31.7%) for both IBS/FD. Among IBS patients, 12/29 (41.4%) fulfilled the diagnostic criteria for IBS-C, 11 (37.9%) for IBS-D, 3 (10.3%) for IBS-M, and 3 (10.3%) for IBS-U.

Among FD patients, 4/36 (11.1%) fulfilled the diagnostic criteria for PDS, 19 (52.8%) for EPS, and 13 (36.1%) for both PDS and EPS. The mean FIQR score at enrolment was 80.9±18.8. Eighteen/60 (30%) and 37/60 (61.7%) reported a "severe disease activity" and "a very severe disease activity" at FIQR, respectively. The severity of FIQR was not associated with the presence of any DGBI (χ^2 1.04; p=0.8). No significant Spearman correlation was found between age and FIQR score at

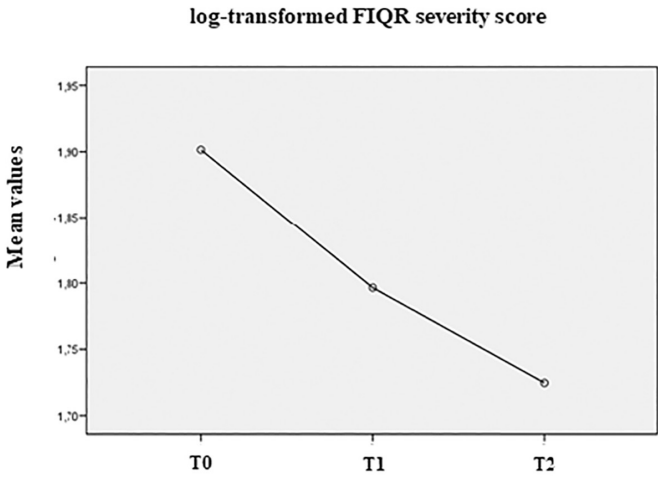

Fig. 2. The mean log-transformed FIQR severity score during the month-to-month comparison period, evaluated at baseline (T0), 3 months after therapy with MC (T1), and 6 months after therapy with medical cannabis (T2).

enrolment (Rs=0.1; p=0.9). The mean weekly number of evacuations and BSFS were 8±4.3 and 3.9±0.9, respectively.

Figure 1 showed both upper (epigastric pain, epigastric burning, postprandial fullness, early satiety) (Fig. 1a) and lower GI (abdominal pain, abdominal distension, and bloating) symptom scores (Fig 1b) at baseline (T0), categorised as absent, mild, and severe.

No significant Spearman correlation was found between the FIQR score and the intensity frequency scores of both upper and lower GI symptoms.

Follow-up evaluation

T1 evaluation. Fifty-two/60 (87%) of FM patients completed the 3 months of treatment with Bedrocan®. The median dose of cannabis used 20 drops/day (equivalent to 20 mg/day). Four patients were lost to follow-up; 4 patients spontaneously interrupted the MC therapy, reporting no therapeutic effects, and refused to fill in the questionnaires. No side effects were reported.

The mean FIQR score at T1 was 65.4±22.6. The prevalence of FM patients reporting "a very severe disease activity" at FIQR was significantly lower than at baseline (61.7 vs 30.8%, p=0.02).

The proportion of patients who reached remission according to FIQR score at T1 was 2/60 (3.3%) in the intention-to-treat analysis and 3.8% in the per-protocol analysis. The mean weekly number of evacuations and BSFS were 8.6±5.0 and 3.9±1.1, respectively.

T2 evaluation. Forty-eight/60 (80%) of FM patients completed the 6 months of treatment with Bedrocan®. One patient did not return for the T6 follow-up visit and did not answer phone calls; 3 subjects interrupted the MC therapy for side effects (confusion and drowsiness).

The mean FIQR score at T2 was 56.6±22.5. The prevalence of FM patients reporting "a very severe disease activity" at FIQR significantly decreased compared to T1 evaluation (30.8% *vs*. 14.6%, p=0.001).

The proportion of patients who reached remission according to FIQR score at T1 was 5/60 (8.3%) in the intention-to-treat analysis and 10.4% in the per-protocol analysis. The mean weekly number of evacuations and BSFS were 8.8±5.3 and 3.9±1.0, respectively.

Months-by-month comparisons. The FIQR severity score log-transformed significantly decreased during the months-by-month comparison period (p<0.001) (Fig. 2).

Among upper GI symptoms, the log-transformed intensity-frequency score of epigastric pain and epigastric burning significantly decreased during the month-by-month comparison period (p<0.001) (Fig. 3). No significant changes in the epigastric fullness and early satiety intensity-frequency score were revealed during the month-by-month comparison period.

Among lower GI symptoms, the log-transformed intensity-frequency score of abdominal pain, abdominal distension, and bloating significantly decreased during the month-by-month comparison period (p<0.01) (Fig. 4). No significant changes were found in BSFS values during the month-by-month comparison period.

Discussion

The present study described the effect of Bedrocan®, a MC compound,

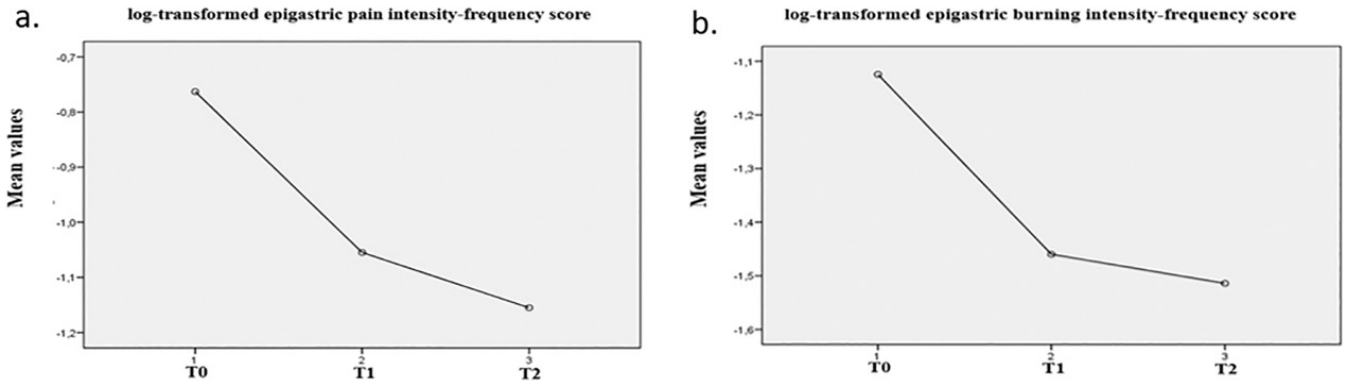

Fig. 3. The log-transformed intensity-frequency score of epigastric pain (**a**) and epigastric burning (**b**) during the months-by-month comparison period, evaluated at baseline (T0), 3 months after therapy with MC (T1), and 6 months after therapy with medical cannabis (T2).

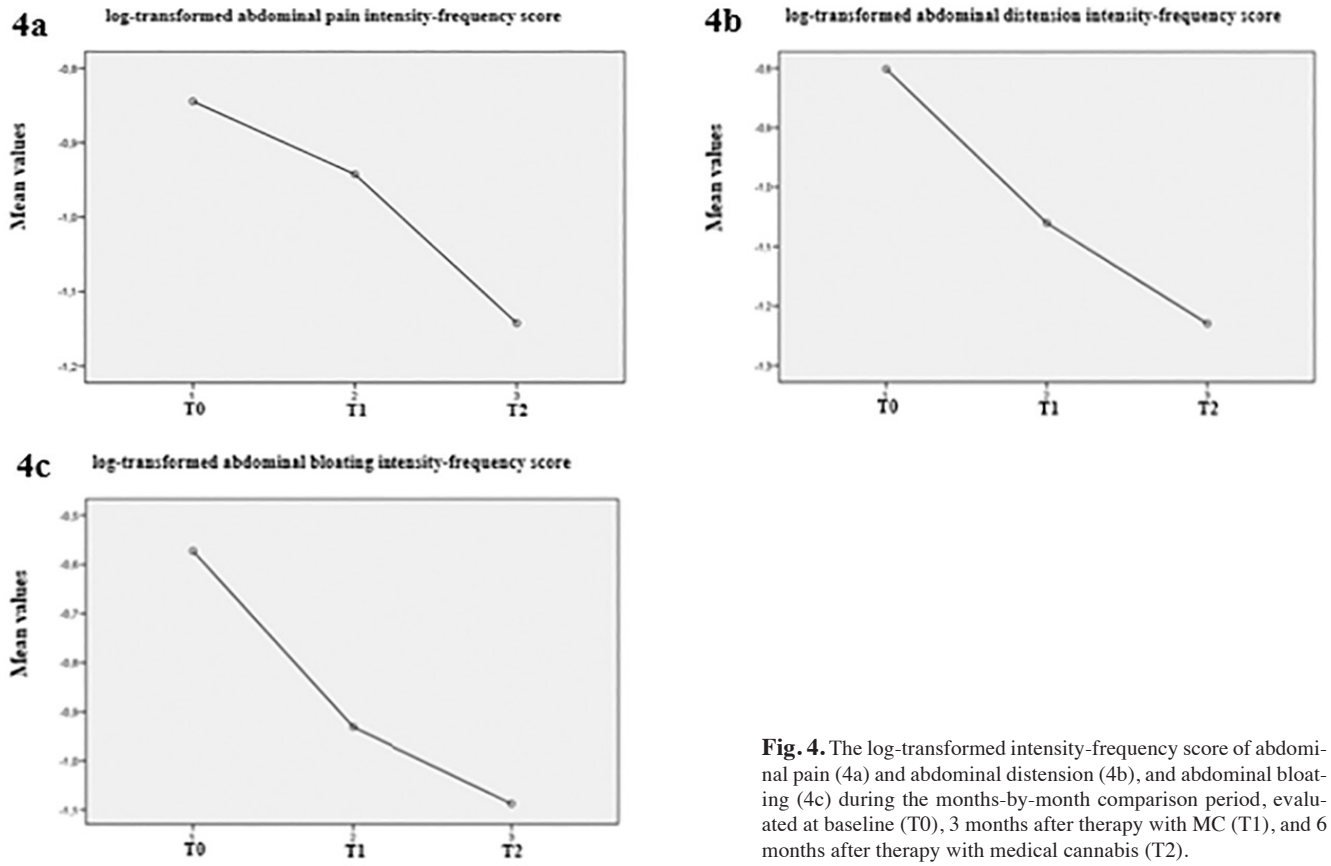

Fig. 4. The log-transformed intensity-frequency score of abdominal pain (4a) and abdominal distension (4b), and abdominal bloating (4c) during the months-by-month comparison period, evaluated at baseline (T0), 3 months after therapy with MC (T1), and 6 months after therapy with medical cannabis (T2).

on gastrointestinal symptoms among FM patients. To our knowledge, this is the first study in which changes in the intensity-frequency of GI symptoms before and during the treatment with MC are reported, using validated questionnaires.

Data about the effect of MC on FM symptoms are still conflicting. A recent systematic review (19) analysed the results of four randomised controlled trials (RCT) and five observational studies evaluating the effect of MC on FM symptoms. All the considered studies, except for one RCT, demonstrated an improvement of FM symptoms with MC. However, the pain evaluation methods, route of administration, and follow-up of patients were different. The authors concluded that, although current evidence is limited, MC appears to be a safe alternative for treating FM. Our results were key with these data and demonstrated that the therapeutic effects continued over time; the FIQR severity score and the percentage of patients reporting "a very severe disease activity" decreased over time during the 6 months of follow-up under Bedrocan® treatment.

Interestingly, we demonstrated a significant reduction in epigastric pain and epigastric burning in FM patients 3 and 6 months after the starting of MC therapy. In contrast, no significant effects were observed for postprandial fullness and early satiety. We previously demonstrated that FD was extremely prevalent and affected up to 80% of FM patients (16). In this paper, we showed a significant reduction of some FD cardinal symptoms, such as epigastric pain and epigastric burning, already after 3 months of therapy with Bedrocan® MC, with a therapeutic effect prolonged during the 6 months of treatment.

Literature data about the effect of MC on dyspepsia are still scanty and conflicting. McCallum *et al*. (26) demonstrated that THC delays the gastric emptying of solid food in humans; however, other studies (27,28) described an improvement of symptoms in patients with idiopathic or diabetic gastroparesis with cannabis use. It has been hypothesized that this improvement in symptoms could be related to cannabis effects on visceral sensation rather than on slowing gastric emptying (29). A recent RCT (30) evaluated the effects of a 4-week treatment with CBD (at an FDA-approved dosage of 20 mg/kg/die) in FD patients with non-delayed gastric emptying, demonstrating that there were no significant improvements in treated patients. However, these results are difficult to compare with those of our study, considering that we used an association of THC and CBD and that the patient's follow-up was different (4 weeks vs 6 months).

Another important finding of this study is the significant decrease in the intensity-frequency score of all the examined lower GI symptoms (abdominal pain, abdominal distension, and bloating) during the therapy with Bedrocan®. The components of Bedrocan® are THC and CBD in a different concentration, which are able to act on CB1 and CB2 receptors. CB1 is one of the most abundant G-protein-coupled receptors in the brain, which highlights

its importance in controlling central neurotransmission. It is also most abundantly in the gut and in the enteric nervous system (31).

CB2 is found on enteric neurons and also expressed by immune and epithelial cells in the GI tract especially in pathological conditions, such as inflammation in which seems to play a role also in the modulation of visceral sensitivity and pain (31, 32).

Activation of these receptors can regulate several functions of the GI tract and CB1 is able to control gastric secretion, gastric emptying, and intestinal motility (31, 32), while CB2 is involved in cell movement, phagocytosis, and immunomodulatory activity (33).

To date, the effect of THC on GI motility has been studied in vivo and ex vivo, mainly on animals (31). THC slowed the gastrointestinal transit of a charcoal meal in live mice (34) and inhibited the contractile response of the isolated guinea pig ileum to electrical and 5-HT stimulation (35). Moreover, in vitro studies on Caco-2 cells suggested the role of THC and CBD in improving intestinal barrier integrity, mainly through CB1 receptor stimulation (36,37). Considering that the preclinical research shows the potential beneficial effects of cannabinoids on GI symptoms, previous studies explored the possible role of cannabinoids in treating GI complaints, particularly IBS. Some authors, in fact, proposed endocannabinoid deficiency as a possible pathophysiological mechanism underlying many IBS manifestations (21). In a review of 2020 by Pandey *et al*. (38) the authors confirmed the role of the eCS in IBS; however, they stated that the lack of controlled trials with cannabinoid agents in IBS precludes making any conclusions on their efficacy in IBS. More recently, a placebo-controlled trial (39) evaluating the usage of cannabidiol chewing gum (containing 50 mg of CBD) in patients with IBS failed to find any significant beneficial effects on pain or quality of life, compared to placebo. Considering that *in vivo* and *in vitro* studies have shown the inhibitory effect of cannabinoid on colonic contractility (40,41), it has been hypothesised a different effect of eCS in the IBS subtypes. In 40 patients with IBS-D and IBS-M, dronabinol, a CB1 and CB2 agonist, significantly increased colonic compliance and decreased colonic motility (42). In our study, we did not find at month-by-month comparisons any significant differences in the trend of intensity-frequency scores of the examined lower GI symptoms across the IBS subtypes. However, we have to consider the small size of our IBS population.

Another perplexing issue is the duration of cannabis treatments, considering that previous studies suggested an increased risk of adverse side effects and, conversely, the possible development of tolerance or dependence state, possibly due to downregulation, internalization and/or desensitisation of endocannabinoid receptors (19). In our study, 3 patients have interrupted the MC therapy at 6 months evaluation for side effects (confusion and drowsiness). Dizziness and drowsiness are among the most common side effects of cannabis (19); however, according to previous studies, we did not report severe adverse side effects associated with cannabinoids treatment (19). Although previous studies reported a possible decrease in Lower oesophageal Sphincter pressure during cannabis treatment (29), we did not reveal any increase in reflux symptoms; in fact, the intensity-frequency scores of heartburns and regurgitation did not significantly change over time. Moreover, the stool consistency, evaluated using the BSFS, was similar before and during the treatment with MC. We hypothesised that while MC may positively influence visceral hypersensitivity and pain perception (thereby improving subjective GI symptoms such as abdominal pain and bloating), it may not have a significant effect on bowel motility, which could explain the lack of change in bowel frequency and stool form.

This study has several limitations, such as the small sample size and the lack of a control group. Hence, further randomised placebo control clinical trials with a higher number of participants should be needed better to assess the role of MC on FM symptom reduction. However, it's the first study evaluating GI symptoms in FM patients with a standardised questionnaire, before and during treatment with a specific strain of cannabis, with a regular assessment of clinical changes and side effects at regular follow-up visits. Based on the knowledge of the role of eCB system in the control of the GI tract, there are some important directions to consider in developing therapeutic strategies to modulate eCB. First, CB1 antagonists at the peripheral level are likely to increase intestinal motility and possibly reduce intestinal permeability, features that could make them therapeutically useful, especially in view of their beneficial effects in patients with FM. CB2 agonists could reduce inflammation in the gastrointestinal tract and limit abnormally accelerated motility.

Conclusions

Despite promising results about the usage of MC in FM patients, there is still much to know and explore about the pathogenetic link between FM and DGBI. Other studies, possibly RCT with longer follow-up, are required. Moreover, these data could encourage further research about the role of MC in the modulation of GI symptoms in DGBI patients.

References

1. CLAUW DJ: Fibromyalgia and related conditions. *Mayo Clin Proc* 2015 ;90(5): 680-92. https://doi.org/10.1016/j.mayocp.2015.03.014
2. SLUKA KA, CLAUW DJ: Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience* 2016; 338: 114-29. https://doi.org/10.1016/j.neuroscience.2016.06.006
3. NIJS J, GEORGE SZ, CLAUW DJ *et al*.: Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet Rheumatol* 2021; 3(5): e383-92. https://doi.org/10.1016/S2665-9913(21)00032-2
4. HÄUSER W, FITZCHARLES MA: Facts and myths pertaining to fibromyalgia. *Dialogues Clin Neurosci* 2018; 20(1): 53-62. https://doi.org/10.31887/DCNS.2018.20.1/whauser
5. WOLFE F, ROSS K, ANDERSON J, RUSSELL IJ, HEBERT L: The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995; 38(1): 19-28. https://doi.org/10.1002/art.1780380105
6. MORENO-FERNÁNDEZ AM, JIMÉNEZ-CASTELLANOS E, IGLESIAS-LINARES A, BUESO-MADRID D, FERNÁNDEZ-RODRÍGUEZ A, DE MIGUEL M: Fibromyalgia syndrome and temporomandibular disorders with muscular pain. A review. *Mod Rheumatol* 2017; 27(2):

210-6. https://doi.org/10.1080/14397595.2016.1193003
7. FERAHMAN D, BUCAK ÖF, ARIK S, ŞAHBAZ T: The hidden burden of fibromyalgia: exploring work impairment and quality of life in caregivers. *Clin Exp Rheumatol* 2025; 43(6): xxx-xxx. https://doi.org/10.55563/clinexprheumatol/obdrlt
8. DROSSMAN DA: Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 2016; 150(6) :1262-1279.e2. https://doi.org/10.1053/j.gastro.2016.02.032
9. DROSSMAN DA, HASLER WL: Rome IV—Functional GI disorders: disorders of gut-brain interaction. *Gastroenterology* 2016; 150(6): 1257-61. https://doi.org/10.1053/j.gastro.2016.03.035
10. VEALE D, KAVANAGH G, FIELDING JF, FITZGERALD O: Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process? *Rheumatology* 1991; 30(3): 220-2. https://doi.org/10.1093/rheumatology/30.3.220
11. SPERBER AD, ATZMON Y, NEUMANN L *et al*.: Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. *Am J Gastroenterol* 1999; 94(12): 3541-6. https://doi.org/10.1111/j.1572-0241.1999.01506.x
12. KURLAND JE, COYLE WJ, WINKLER A, ZABLE E: Prevalence of irritable bowel syndrome and depression in fibromyalgia. *Dig Dis Sci* 2006; 51(3): 454-60. https://doi.org/10.1007/s10620-006-3143-0
13. LUBRANO E, IOVINO P, TREMOLATERRA F, PARSONS WJ, CIACCI C, MAZZACCA G: Fibromyalgia in patients with irritable bowel syndrome: an association with the severity of the intestinal disorder. *Int J Colorectal Dis* 2001; 16(4): 211-5. https://doi.org/10.1007/s003840100317
14. IOVINO P, TREMOLATERRA F, CONSALVO D, SABBATINI F, MAZZACCA G, CIACCI C: Perception of electrocutaneous stimuli in irritable bowel syndrome. *Am J Gastroenterol* 2006; 101(3): 596-603. https://doi.org/10.1111/j.1572-0241.2006.00401.x
15. TREMOLATERRA F, GALLOTTA S, MORRA Y, LUBRANO E, CIACCI C, IOVINO P: The severity of irritable bowel syndrome or the presence of fibromyalgia influencing the perception of visceral and somatic stimuli. *BMC Gastroenterol* 2014; 14: 182. https://doi.org/10.1186/1471-230X-14-182
16. SETTEMBRE C, D'ANTONIO E, MOSCATO P, LOI G, SANTONICOLA A, IOVINO P: Association among disorders of gut-brain interaction (DGBI) and fibromyalgia: a prospective study. *J Clin Med* 2022; 11(3): 809. https://doi.org/10.3390/jcm11030809
17. MARTINEZ JE, GUIMARÃES I: Fibromyalgia – are there any new approaches? *Best Pract Res Clin Rheumatol* 2024; 101933. https://doi.org/10.1016/j.berh.2024.101933.
18. DI CARLO M, BIANCHI B, SALAFFI F *et al*.: Fibromyalgia: one year in review 2024. *Clin Exp Rheumatol* 2024; 42(6): 1141-9. https://doi.org/10.55563/clinexprheumatol/mbyi1n
19. STRAND NH, MALONEY J, KRAUS M *et al*.: Cannabis for the treatment of fibromyalgia: a systematic review. *Biomedicines* 2023; 11(6): 1621. https://doi.org/10.3390/biomedicines11061621
20. STORR MA, YÜCE B, ANDREWS CN, SHARKEY KA: The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome. *Neurogastroenterol Motil* 2008; 20(8): 857-68. https://doi.org/10.1111/j.1365-2982.2008.01175.x
21. SMITH SC, WAGNER MS: Clinical endocannabinoid deficiency (CECD) revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol Lett* 2014; 35(3): 198-201.
22. BRIERLEY SM, GREENWOOD-VAN MEERVELD B, SARNELLI G, SHARKEY KA, STORR M, TACK J: Targeting the endocannabinoid system for the treatment of abdominal pain in irritable bowel syndrome. *Nat Rev Gastroenterol Hepatol* 2023; 20(1): 5-25. https://doi.org/10.1038/s41575-022-00688-3
23. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016; 46(3): 319-29. https://doi.org/10.1016/j.semarthrit.2016.08.012
24. OLIVIERO G, RUGGIERO L, D'ANTONIO E *et al*.: Impact of COVID-19 lockdown on symptoms in patients with functional gastrointestinal disorders: relationship with anxiety and perceived stress. *Neurogastroenterol Motil* 2021; 33(5): e14092. https://doi.org/10.1111/nmo.14092
25. SALAFFI F, DI CARLO M, BAZZICHI L *et al*.: Definition of fibromyalgia severity: findings from a cross-sectional survey of 2339 Italian patients. *Rheumatology* 2021; 60(2): 728-36. https://doi.org/10.1093/rheumatology/keaa342
26. MCCALLUM RW, SOYKAN I, SRIDHAR KR, RICCI DA, LANGE RC, PLANKEY MW: Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. *Aliment Pharmacol Ther* 1999; 13(1): 77-80. https://doi.org/10.1046/j.1365-2036.1999.00419.x
27. BARBASH B, MEHTA D, SIDDIQUI MT, CHAWLA L, DWORKIN B: Impact of cannabinoids on symptoms of refractory gastroparesis: a single-center experience. *Cureus* 2019; 11(12): e6430. https://doi.org/10.7759/cureus.6430
28. PARKMAN HP, SHARKEY EP, NGUYEN LA *et al*.: Marijuana use in patients with symptoms of gastroparesis: prevalence, patient characteristics, and perceived benefit. *Dig Dis Sci* 2020; 65(8): 2311-20. https://doi.org/10.1007/s10620-019-05784-0
29. CAMILLERI M, ZHENG T: Cannabinoids and the gastrointestinal tract. *Clin Gastroenterol Hepatol* 2023; 21(13): 3217-29. https://doi.org/10.1016/j.cgh.2023.06.036
30. ATIEH J, MASELLI D, BREEN-LYLES M *et al*.: Cannabidiol for functional dyspepsia with normal gastric emptying: a randomized controlled trial. *Am J Gastroenterol* 2022; 117(8): 1296-304. https://doi.org/10.14309/ajg.0000000000001836
31. ALHOUAYEK M, MUCCIOLI GG: COX-2-derived endocannabinoid metabolites as novel inflammatory mediators. *Trends Pharmacol Sci* 2014; 35(6): 284-92. https://doi.org/10.1016/j.tips.2014.03.006
32. WRIGHT K, ROONEY N, FEENEY M *et al*.: Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. *Gastroenterology* 2005; 129(2): 437-53. https://doi.org/10.1053/j.gastro.2005.05.026
33. CROWLEY K, KIRAGA Ł, MISZCZUK E *et al*.: Effects of cannabinoids on intestinal motility, barrier permeability, and therapeutic potential in gastrointestinal diseases. *Int J Mol Sci* 2024; 25(12): 6682. https://doi.org/10.3390/ijms25126682
34. ANDERSON PF, JACKSON DM, CHESHER GB: Interaction of delta9-tetrahydrocannabinol and cannabidiol on intestinal motility in mice. *J Pharm Pharmacol* 1974; 26(2): 136-7. https://doi.org/10.1111/j.2042-7158.1974.tb09281.x
35. PERTWEE RG, STEVENSON LA, ELRICK DB, MECHOULAM R, CORBETT AD: Inhibitory effects of certain enantiomeric cannabinoids in the mouse vas deferens and the myenteric plexus preparation of guinea-pig small intestine. *Br J Pharmacol* 1992; 105(4): 980-4. https://doi.org/10.1111/j.1476-5381.1992.tb09076.x
36. ALHAMORUNI A, LEE AC, WRIGHT KL, LARVIN M, O'SULLIVAN SE: Pharmacological effects of cannabinoids on the Caco-2 cell culture model of intestinal permeability. *J Pharmacol Exp Ther* 2010; 335(1): 92-102. https://doi.org/10.1124/jpet.110.171025
37. ALHAMORUNI A, WRIGHT KL, LARVIN M, O'SULLIVAN SE: Cannabinoids mediate opposing effects on inflammation-induced intestinal permeability. *Br J Pharmacol* 2012; 165(8): 2598-610. https://doi.org/10.1111/j.1476-5381.2011.01693.x
38. PANDEY S, KASHIF S, YOUSSEF M *et al*.: Endocannabinoid system in irritable bowel syndrome and cannabis as a therapy. *Complement Ther Med* 2020; 48: 102242. https://doi.org/10.1016/j.ctim.2019.102242
39. VAN ORTEN-LUITEN ACB, DE ROOS NM, MAJAIT S, WITTEMAN BJM, WITKAMP RF: Effects of cannabidiol chewing gum on perceived pain and well-being of irritable bowel syndrome patients: a placebo-controlled crossover exploratory intervention study with symptom-driven dosing. *Cannabis Cannabinoid Res* 2022; 7(4): 436-44. https://doi.org/10.1089/can.2021.0161
40. HORNBY PJ, PROUTY SM: Involvement of cannabinoid receptors in gut motility and visceral perception. *Br J Pharmacol* 2004; 141(8): 1335-45. https://doi.org/10.1038/sj.bjp.0705724
41. BASHASHATI M, NASSER Y, KEENAN CM *et al*.: Inhibiting endocannabinoid biosynthesis: a novel approach to the treatment of constipation. *Br J Pharmacol* 2015; 172(12): 3099-111. https://doi.org/10.1111/bph.13082
42. WONG BS, CAMILLERI M, BUSCIGLIO I *et al*.: Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. *Gastroenterology* 2011; 141(5): 1638-47.e1-7. https://doi.org/10.1053/j.gastro.2011.07.043