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Brief Report

Oral Cannabinoid Preparations for the Treatment of Chronic Migraine: A Retrospective Study

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Abstract

Objective. To explore the effectiveness and safety of three oral cannabinoid preparations (FM2®, Istituto farmaceutico militare, Firenze, Italy; Bedrocan®, Bedrocan International, Vandaam, Netherlands; and Bediol®, Bedrocan International, Vandaam, Netherlands) in the treatment of chronic migraine. **Design**. Retrospective, cohort study. **Subjects**. Patients with chronic migraine who received FM2, Bedrocan, or Bediol daily for the off-label treatment of their headache, for up to 6 months. **Methods**. The number of migraine days per month, pain intensity, the number of acute medications taken per month, the number of days per month on which the patient took at least one acute medication, and adverse events were recorded at baseline and at 3 months and 6 months after the start of treatment with oral cannabinoid preparations. **Results**. The number of migraine days did not change significantly after the third month or the sixth month when compared with baseline ($P = 0.1182$). The pain intensity ($P = 0.0004$), the acute medication consumption ($P = 0.0006$), and the number of days per month in which patients took at least one acute medication significantly decreased when compared with baseline ($P = 0.0004$). No significant differences were found between patients who were still taking a preventive treatment for chronic migraine and those who were not (all $P > 0.05$). Different oral cannabinoid preparations displayed similar levels of effectiveness (all $P > 0.05$). The adverse events were mostly mild and occurred in 43.75% of patients. **Conclusions**. Oral cannabinoid preparations may have a role in reducing pain intensity and acute medication intake in patients with chronic migraine, but the magnitude of the effect seems modest; further studies are needed.

Key Words: Chronic Migraine; Endocannabinoid System; Δ9-Trans-Tetrahydrocannabinol; Cannabidiol; Number of Migraine Days; Acute Medication Consumption

Introduction

The endocannabinoid system (ECS) consists of endocannabinoids, their receptors, and the enzymes responsible for their synthesis and degradation [1]. Arachidonoylethanolamide (AEA) and 2-arachidonoyglycerol (2-AG) are the best-characterized endocannabinoids and act primarily upon cannabinoid receptor type 1 (CB1) and 2 (CB2) [2]. CB1 is mainly presynaptic and acts as a tonic inhibitor of the release of various neurotransmitters, whereas CB2 is expressed mainly on immune cells and is thought to exert immunosuppressive effects [2]. CB1 and CB2 heterodimerize with each other and with different receptors, thus allowing endocannabinoids to influence different pathways [2]. Hence, the pharmacological modulation of the ECS may be a valuable tool for many conditions, such as pain [3, 4]. Indeed, a role for the ECS has been proposed in migraine [5]. Chronic migraine (CM) tremendously lowers patients' quality of life and frequently forces patients to take a large amount of acute medications, thus worsening CM and putting them at risk of developing drug-related adverse events (AEs) [6]. The peripheral and central sensitization of the trigeminal system is crucial for CM pathophysiology [7], and moreover, animal studies suggest that acute medication overuse may worsen this phenomenon [8]. As a whole, endocannabinoids could relieve the trigeminal sensitization underlying CM: In animal models of trigeminal pain, AEA inhibits trigeminal neurons [9, 10], acting upon CB1 [11]. AEA also inhibits trigeminal input transmission by acting on CB1 and serotonin receptor types 1B and 1D in the brain stem after the electrical stimulation of the dura mater in rats [12]. Furthermore, AEA was proved to exert an analgesic effect in a mouse model of nitroglycerin-induced trigeminal pain [13]. In clinical settings, a reduction of the ECS tone has been suggested in patients with CM, as they have lower concentrations of AEA in the cerebral-spinal fluid than do healthy controls [14]. Additionally, AEA and 2-AG degradation is reduced in patients with CM as compared with patients with episodic migraine , thus suggesting an adaptive behavior to endocannabinoid deficiency [15]. Moreover, the lower endocannabinoid degradation rate seems to be relieved when patients with CM undergo an acute medication withdrawal [16]. With this taken into consideration, an attractive therapeutic approach could be the administration of phytocannabinoids in these patients to relieve the endocannabinoid deficiency. Phytocannabinoids, such as the best-characterized Δ9-trans-tetrahydrocannabinol (THC) and cannabidiol (CBD), are found in *Cannabis sativa L* plants [17]. The Italian Ministry of Health approved the medical use of cannabinoid formulations to treat chronic pain in 2018 [18]. The aim of the present study is to assess the effectiveness and safety of different oral cannabinoid preparations for the treatment of CM.

Methods

Design

This retrospective cohort study was conducted at the headache center of the University of Modena and Reggio Emilia in Modena, Italy.

Patients and Drugs

Patients with CM who received an oral cannabinoid preparation for the treatment of their headache between January 1, 2019, and December 31, 2019, were considered. Oral cannabinoid preparations were prescribed as an off-label additional treatment for CM but only when the patient did not respond to other first- or second-line recommended preventive treatments [19] (because of inefficacy or AEs) or when such treatments were contraindicated. As oral cannabinoid preparations were not recommended in the latest version of the Italian guidelines for the treatment of primary headaches [19], every patient had to sign an informed consent agreement for the off-label use before treatment could be started. Three different formulations were prescribed: FM2® (titrated at 5–8% of THC and 7.5–12% of CBD), Bediol® (titrated at 6.5% of THC and 8% of CBD), and Bedrocan® (titrated at 19–22% of THC and <1% of CBD) [20]. The drugs were made as galenic preparations in olive oil and checked for the correct titration by a trained pharmacist using liquid chromatography tandem mass spectrometry, following Italian guidelines [20]. As there were no recommended dosages for the treatment of patients with CM, a maximum dose of 1 mL (≈25 drops) daily was prescribed to minimize the risk of AEs [21]. The minimum prescribed dose was 10 drops daily. Each single patient took only one type of oral cannabinoid preparation and at a stable dose during the observational period. Patients who were still taking other type(s) of preventive treatments were allowed to continue them throughout the study at a stable dose. The study was approved by the AVEN Ethics Committee (protocol number: 144/2020/OSS/AOUMO). All patients signed an informed consent agreement for study participation and data publication.

Analyzed Variables

The analyzed variables were derived from the past medical records owned by the institution in which the study was performed. The following demographic variables were collected: age, sex, comorbidities, type(s) of acute medication(s) taken at baseline, preventive treatment(s) used other than oral cannabinoid preparations, previous preventive treatments to which patients did not respond, type of cannabinoid preparation taken, and dosage. Moreover, the following migraine features were collected: the number of migraine days per month (monthly migraine days [MMD]), the pain intensity score on the numeric rating scale (NRS), the number of acute

medications taken per month (acute medication consumption [AC]), the number of days per month on which the patient took at least one acute medication (number of days on medication [NDM]). These variables were collected at the beginning of the treatment (baseline), as well as 3 and 6 months later. Moreover, the length of migraine history, the length of CM, and the existing characteristics of migraine were collected at the baseline. The number and type of AEs reported by patients were descriptively analyzed.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, whereas categorical ones were expressed as subject counts and percentages. Continuous variables were compared with the one-way analysis of variance followed by the Tukey-Kramer post hoc comparison test. Categorical variables were compared with the chi-squared test for the homogeneity of odds. Sample calculation was not done because this study was performed on available data. However, the calculated power of the study was 1 and was calculated by the adoption of an $\alpha = 0.05$, a sample size of 32, and a threshold reduction in the baseline MMD of 50% after 6 months of treatment (a threshold reduction in MMD usually considered to rule out the placebo effect [19]). A P value lower than 0.05 was considered significant. All calculations were performed with the STATA/IC version 15.1 software (StataCorp LLC, College Station, TX, USA).

Results

Data on 32 patients were analyzed. Demographic data are summarized in Table 1.

Compared with the baseline, the MMD did not improve significantly after 3 months or after 6 months ($P = 0.1182$). The NRS score significantly decreased after both 3 and 6 months of treatment as compared with baseline ($P < 0.0001$). The AC significantly decreased after 3 months and after 6 months of treatment as compared with the baseline ($P = 0.0006$), and the NDM followed the same trend ($P = 0.0004$). No significant differences were noticed with regard to MMD, AC, NRS score, and NDM between the third and the sixth months of treatment (all $P > 0.05$). The proportion of patients with nausea or vomiting during attacks significantly decreased after 6 months of treatment ($P = 0.0057$), again with no significant differences between the third and the sixth months. These data are summarized in Table 2.

The comparison of patients who were taking a preventive treatment and the ones who were not revealed similar values of MMD (25.47 ± 7.07 vs 24 ± 8.77, $P = 0.6095$), AC (29.47 ± 16.88 vs 42.06 ± 62.09, $P = 0.4534$), NRS score (7.33 ± 0.82 vs 7 ± 1.54, $P = 0.4596$), and NDM (22.33 ± 8.83 vs 18.65 ± 11.11, $P = 0.3118$) after 3 months. No significant differences were noticed with regard to MMD (24.92 ± 7.99 vs 25.4 ± 7.94, $P = 0.8767$), AC (19.25 ± 9.21 vs 30.67 ± 36.11, $P = 0.2975$), NRS score (6.91 ± 1 vs 6 ± 1.56, $P = 0.0896$), and NMD (18.67 ± 9.47 vs 16.87 ± 10.8, $P = 0.6537$) at the sixth month. Patients taking FM2 and the ones taking Bedrocan displayed similar values of MMD (23.78 ± 8.38 vs 25.77 ± 7.74, $P = 0.5057$), AC (34.22 ± 53.53 vs 40.85 ± 37.86, $P = 0.7054$), NRS score (7.11 ± 1.49 vs 7.31 ± 0.85, $P = 0.673$), and NMD (18.39 ± 10.26 vs 23.92 ± 9.34, $P = 0.1349$) at the third month. At the sixth month, no differences were found with regard to MMD (25.71 ± 7.44 vs 24.3 ± 8.74, $P = 0.7608$), AC (21.18 ± 26.88 vs 33.1 ± 29.06, $P = 0.4887$), NRS score (6.29 ± 1.61 vs 6.6 ± 0.97, $P = 0.7944$), and NDM

Table 1. Demographic features of the studied sample

Variable	Number
Age, years, mean ± SD	51.91 ± 6.51
Female sex, n (%)	27/32 (84.38)
Length of migraine, years, mean ± SD	18.36 ± 9.2
Length of CM, years, mean ± SD	14.31 ± 8.03
Unilateral pain, n (%)	20/32 (62.5)
Pulsating pain, n (%)	27/32 (84.38)
Nausea and/or vomiting, n (%)	30/32 (93.75)
Photophobia and/or phonophobia, n (%)	19/32 (59.38)
Aura, n (%)	3/32 (9.38)
Acute medications overused at the baseline, n (%)	
Triptans	23/32 (71.88)
Sumatriptan	14/32 (43.75)
Eletriptan	7/32 (21.88)
Rizatriptan	2/32 (6.25)
Nonsteroidal anti-inflammatory drugs	19/32 (59.38)
Acetamoniphen	10/32 (31.25)
Ketoprofen	4/32 (12.5)
Ketorolac	2/32 (6.25)
Ibuprofen	1/32 (3.13)
Diclofenac	1/32 (3.13)
Indometacin	1/32 (3.13)
Combination of analgesics	4/32 (12.5)
Paracetamol+ ibuprofen	2/32 (6.25)
Indometacine+ prochlorperazine+ caffeine	1/32 (3.13)
Propiphenazone+ butalbital+ caffeine	1/32 (3.13)
Preventive treatments, n (%)	
Patients still on prophylaxis	17/32 (53.13)
Antidepressants	9/17 (52.94)
Beta-blockers	3/17 (17.65)
Anticonvulsants	5/17 (29.41)
Number of previous preventive treatments tried, mean ± SD	6.8 ± 1.7
Patients with comorbidities, n (%)	27/32 (84.38)
Type of comorbidities, n (%)	
Psychiatric	24/32 (75)
Rheumatological	24/32 (75)
Gastroenterological	10/32 (31.25)
Oral cannabinoid doses	
FM2, mean ± SD	13.28 ± 4.82
Bedrocan, mean ± SD	14 ± 3.21
Bediol, n	15

*Acute medications overused and comorbidities are not addable, because there were patients overusing more than one acute medication or with more than one comorbidity simultaneously.

(15.35 ± 9.44 vs 21.6 ± 10.37, $P = 0.2261$) between patients taking FM2 and patients taking Bedrocan. These data are graphically summarized in Figure 1.

Globally, 14 patients (43.75%) had at least one AE. In 12 cases, the AEs were mild and did not cause treatment discontinuation. Two patients (6.25%) complained

Table 2. MMD, AC, NRS Score, and NDM

Variables	Baseline (n = 32)	After 3 Months (n = 32)	After 6 Months (n = 28)	*P* Value
MMD, mean ± SD	27.88 ± 4.63	24.69 ± 7.92	25.36 ± 7.72	0.1182
NRS, mean ± SD	9.59 ± 0.76	7.16 ± 1.25*	6.43 ± 1.37*	<0.0001
AC, mean ± SD	83.78 ± 88.43	36.16 ± 46.47*	25.04 ± 27.41*	0.0006
NDM, mean ± SD	26.69 ± 6.32	20.38 ± 10.12*	17.39 ± 9.99*	0.0004
Nausea and/or vomiting, n (%)	30/32 (93.75)	20/32 (62.5)	19/32 (59.38)	0.0057
Photophobia and/or phonophobia, n (%)	19/32 (59.38)	19/32 (59.38)	19/32 (59.38)	0.6860

*Significantly different vs baseline.

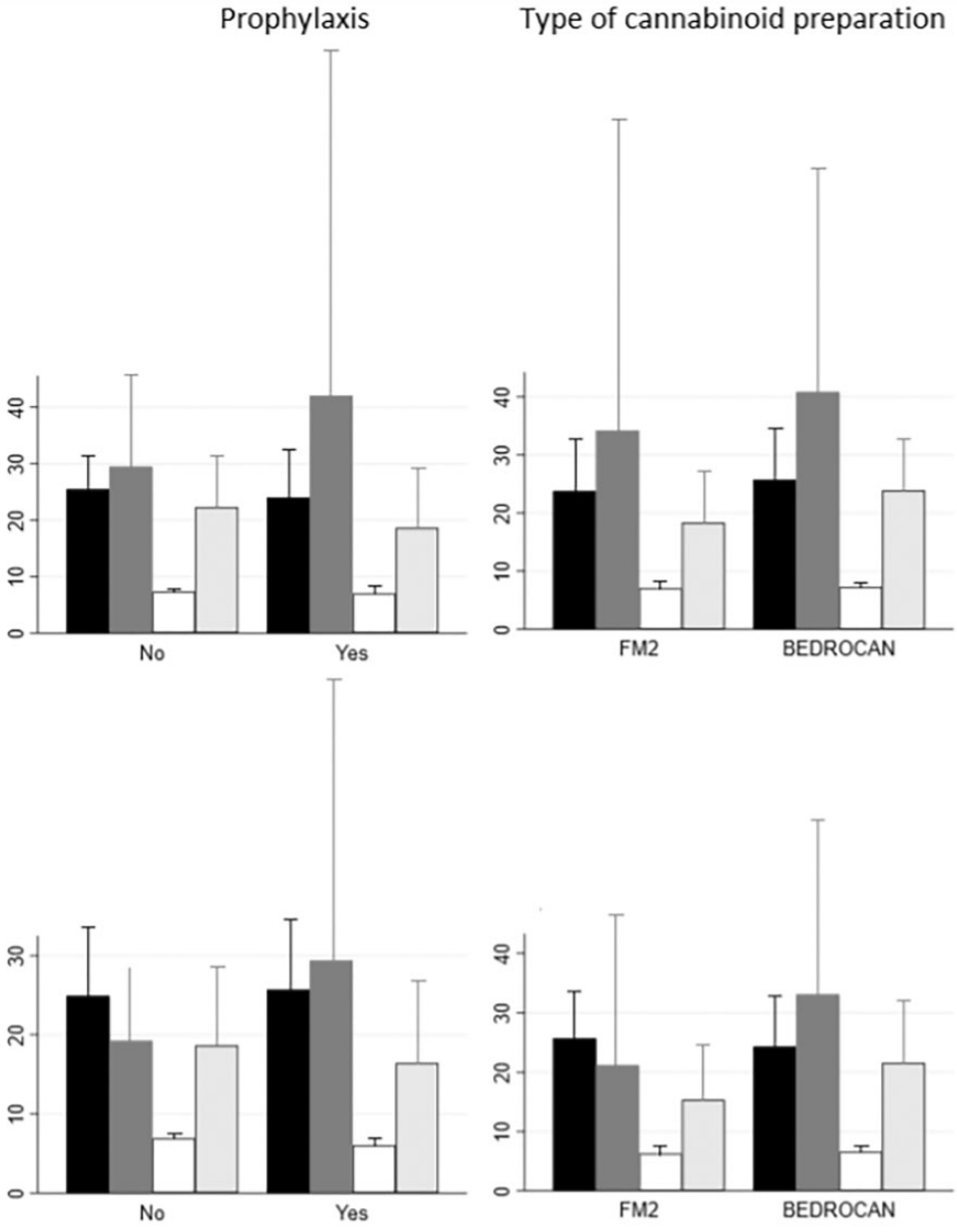

Figure 1. MMD (black bars), AC (dark gray bars), NRS score (white bars), and NDM (light gray bars) values at the third month (top) and at the sixth month (bottom) between patients who were taking a migraine preventive treatment or not and between patients who received FM2 or Bedrocan.

Table 3. Adverse events

Adverse Event	Number of Patients (%)
Drowziness	10/32 (31.25)
Postural instability	2/32 (6.25)
Vertigo	1/32 (3.13)
Weight gain	1/32 (3.13)
Total	14/32 (43.75)

of moderate vertigo, which caused treatment suspension; moderate AEs resolved with therapy suspension. No serious AEs were reported. No differences were noticed in the AE rate with regard to the type of cannabinoid preparation taken (odds ratio [OR] = 1.6, 95% confidence interval [CI]: 0.36–7.05, $P = 0.5309$). Data on AEs are summarized in Table 3.

Discussion

The positive effects of phytocannabinoids in CM are well known by patients, as some take marijuana as a last-resort self-treatment [22]. Indeed, in the present study , oral cannabinoid preparations reduced NRS score, AC, and NDM in this cohort of patients with CM after 3 and 6 months of treatment, as compared with the baseline. Moreover, oral cannabinoid preparations were also able to reduce the proportion of patients with nausea or vomiting during attacks. Notably, these results were achieved in a severely impaired population, as patients had almost daily migraine attacks, took more than one acute medication per day, had a long history of CM, and had not responded to many preventive treatments in the past (Table 1). Furthermore, the analyzed sample displayed a high rate of psychiatric and rheumatological comorbidities (Table 1) that might have reduced the effectiveness of preventive treatment for CM [23] and could have affected the effectiveness of oral cannabinoid preparations, as well.

The high clinical complexity of the analyzed sample could also account for the discrepancies between the present study's results and those of the study conducted by Rhyne and co-workers [24], who detected a significant reduction in the number of headache days per month in a cohort of 121 patients treated with medical marijuana. However, the study by Rhyne et al. assessed people with episodic migraine and a low acute medication intake, who thus gained higher clinical benefits from cannabinoid administration [24]. The lack of a significant reduction of the MMD in the present study could be attributable to the worse impairment of patients at the baseline and reflects the central action of the ECS on pain; indeed, the ECS acts as a tonic regulator of the trigeminal system and of those brain areas involved in trigeminal pain perception [4], thus justifying the higher reduction in pain intensity rather than frequency.

The oral cannabinoid preparations used were differently titrated, but all contained THC and CBD. THC is a partial agonist of CB1 and CB2, whereas CBD acts mainly as a CB2 antagonist. The pharmacological profiles of THC and CBD are further complicated by their interactions with other kinds of receptors, such as transient receptor potential ion channels, serotonin receptors, peroxisome-activated proliferating factor receptors, and opioid receptors [2]. Nevertheless, most research has focused on CB1 and CB2. For example, Kandasamy's group [25] demonstrated that intraperitoneally injected THC relieved the inhibition of wheel running induced by the injection of allyl-isothiocyanate into the dura mater of rats, mainly through CB1 receptors. Moreover, the inhibition of meningeal mast cell degranulation through CB1 and CB2 receptors may reduce the sensitization of trigeminal nerve fibers [26]. As THC can pass the blood–brain barrier because of its high lipophilicity [27], it can act on central CB1 receptors, which are widely expressed in the brain areas involved in trigeminal pain control [28], in the emotional processing of pain [29], and in the triggering of nausea [30], thus justifying the positive effect on nausea or vomiting achieved in the present study. On the other hand, preclinical evidence has linked THC administration with trigeminal sensitization. Repeated THC administration induced periorbital allodynia in mice [31]. Despite this, a previous study based on a validated animal model of migraine induced by allyl-isothiocyanate injection into the dura mater demonstrated that repeated THC administration prevented allyl-isothiocyanate–induced wheel running inhibition, and this effect was maintained after repeated administrations [31].

The regular intake of acute medications may worsen CM itself [6]; in the present study, the AC dramatically decreased during the study, but the question of whether the repetitive consumption of oral cannabinoid preparations could cause CM worsening is a matter of debate. Kandasamy's group [32] compared the effects of THC and morphine, demonstrating that wheel running inhibition duration increases with the regular repetition of morphine administration but not with that of THC. The authors concluded that THC was not associated with trigeminal sensitization or that, at least, morphine-induced trigeminal sensitization spreads faster [32]. These results were substantially confirmed by Yamamoto and collaborators [33], who discovered that pretreatment with peripheral-acting cannabinoids prevents all the biochemical correlates of allodynia and trigeminal sensitization in a mouse model of CM and acute medication overuse. This indicates that cannabinoids are less associated with those phenomena of trigeminal sensitization that can aggravate CM, thus suggesting their possible long-term use [33], as the stable reduction of the NRS score achieved seems to indicate.

The same reasoning may be applied to the lack of significant differences in MMD, AC, NRS, and NDM between patients who were already taking a preventive medication and patients who did not take a preventive medication. The analyzed sample was composed of patients unresponsive to the first- and second-line preventive treatments, who did not respond to an average of 6.85 ± 1.7 preventive treatments.

As is well known, the higher the number of failed preventive treatments, the lower will be the therapeutic gain with future ones [34, 35]. Given this, the lack of differences between those patients who received a preventive treatment and patients who did not should not be surprising, as the preventive treatments that were used were, after many years, almost useless. Additionally, no significant differences were found with regard to the analyzed parameters after 3 and 6 months between patients who used FM2 and patients who used Bedrocan. This may sound surprising if one considers their composition: FM2 is titrated at 5–8% of THC and 7.5–12% of CBD, whereas Bedrocan contains 19–22% of THC and less than 1% of CBD [20]. Despite this, the oral absorption rate of THC and CBD is very low [36], thus accounting for a standardization of the plasmatic concentrations and, therefore, of the amount of THC and CBD directly acting upon CB1 and CB2, both centrally and peripherally. This may explain the similar AE rates in patients taking FM2 and those taking Bedrocan, although this consideration may be distorted by the small sample size. Among all patients, the AE rate is high (14/32 [43.75%]). Among preventive treatments for migraine, anticonvulsants have the highest rate of AEs, which limit patients' adherence [37]. The AE rate in the present study is lower than that of anticonvulsants and, moreover, most of displayed AEs were mild, so that the rate of dropouts was low (6.25%). Two patients had to quit treatment after the third month because of moderate vertigo, a known cannabinoid effect [38].

Limitations

This study has many limitations, the main ones being the small sample size, the lack of a control group, and the short period of observation. Moreover, because of its retrospective nature, the numbers of patients taking the different cannabinoid preparations are unbalanced, and only one patient took Bediol, which limits the study's ability to compare the effectiveness and safety of Bediol against FM2 and Bedrocan. Additionally, patients took different dosages, and this may have impacted the results as well; however, this was almost inevitable given that the Italian guidelines do not yet indicate a precise dosage, so the dosages were empirically chosen by every physician. Moreover, the oral cannabinoid preparations lacked formula designations, as their preparation had been done by pharmacies outside the hospital in which the study took place because of regulatory issues [18].

Conclusions

The effectiveness of oral cannabinoid preparations in the treatment of CM seems modest in this study. Nonetheless, the observed improvements in the NRS score, AC, and NDM may suggest a role of oral cannabinoid preparations in patients with CM and high analgesic consumption, as already assessed for another cannabinoid, Nabilone (Bausch Health Companies INC., Laval, Canada) [39]. The lack of significant differences with regard to the MMD may be linked to the high clinical complexity of the analyzed sample, but the aforementioned limitations might have affected the conclusions of the study, as well. The present study does not clearly support the use of oral cannabinoid preparations for the treatment of CM, but with consideration of the cannabinoid-targeted neurobiological mechanisms, these preliminary results may indicate a role of this drug class in the therapeutic armamentarium for CM. To clearly establish the real magnitude of the effect of oral cannabinoid preparations in the treatment of CM, randomized, placebo-controlled studies with big samples are needed .

Authors' Contributions

LP, SG, and AN conceived the study and designed it. Material preparation and data collection were performed by AF, FLC, MMC, and SG. Data analysis was performed by CB. The first draft of the manuscript was written by CB, and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

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