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Study design

Efficacy of Cannabidiol Versus Ibuprofen in the Relief of Menstrual Pain in Females Living with Primary Dysmenorrhea: Phase II, Non-Inferiority trial

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ABSTRACT:

Introduction: Pain is the cardinal symptom in women living with primary dysmenorrhea (PDM), resulting in a relentless negative effect on their quality of life. Women with PDM have higher levels of prostaglandin in their endometrial fluid, which correlates with the degree of pain. The standard of care treatment for pain associated with PDM starts with nonsteroidal anti-inflammatory drugs (NSAIDs) that block prostaglandin-triggering enzymes. Although NSAIDs are a feasible option, they are also associated with a significant risk of side effects. Around 20 to 25% of patients will experience pain refractory to NSAIDs and seek alternative therapies. Cannabidiol (CBD) is a well-tolerated potential therapy for several chronic diseases, including pain, and acts by blocking prostaglandin-triggering enzymes, similar to NSAIDs. The safety of CBD is well established, with the advantage of acting via central and peripheral mechanisms. To date, no previous trials assessing CBD alone for dysmenorrhea have been conducted.

Objective: To evaluate the effect of CBD alone in reducing acute menstrual pain compared to ibuprofen, as assessed by the total pain relief (TOTPAR) scale.

Design: Randomized (with random block sizes), triple-blinded, multicenter, parallel-group, non-inferiority clinical trial.

Participants: PDM patients aged 18 to 40 years, with regular menstrual cycles (ranging from 21 to 35 days) and a visual analog scale (VAS) score of ≥ 5.

Intervention: 108 patients will be randomized with an allocation ratio of 1:1 to either CBD 200 mg/day or ibuprofen 800 mg/day. The sample size is based on a mean expected pain relief for ibuprofen of 16.49 and CBD of 14.02, as assessed by the TOTPAR scale and on a 30% estimated dropout rate.

Main Outcomes Measures: The primary outcome will be the mean difference in the TOTPAR scale (range, 0-4) after taking the study drugs over four menstrual cycles. TOTPAR will be assessed after 1, 2, 3, 4, 5, and 6 hours after taking the study drugs. Secondary outcomes include pain VAS, adverse events, the need for breakthrough medications, and quality of life (QoL).

Discussion: NSAIDs may cause troubling side effects, and CBD is well tolerated in clinical trials, with acceptable adverse event profiles. Numerous randomized clinical trials have demonstrated the safety and efficacy of CBD in alleviating other central and peripheral pain disorders. The results of this trial aim to provide much-needed evidence that oral CBD alone is an alternative for treating menstrual pain in women with PDM. CBD represents an important promise for women with PDM who do not respond or have contraindications to NSAIDs.

Keywords: Cannabidiol, CBD, menstrual pain, ibuprofen, pain relief, non-inferiority, dysmenorrhea

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Introduction

Pain is the cardinal symptom in women suffering from primary dysmenorrhea (PDM), with a high impact on their quality of life. Studies have shown that the prevalence of PDM in adolescent and young women varies from 34% to 94% (De Sanctis et al., 2016), which renders it one of the most under-appreciated medical conditions for women at a fertile age. The most common symptoms are lower abdominal or pelvic pain that usually lasts from 8 to 72 hours, beginning at the onset of menstrual flow. The available literature suggests that endometrial cells release prostaglandins, mainly Prostaglandin F2 (PGF2), a uterine stimulant. The higher levels of prostaglandin in the endometrial fluid - that occurs during day one and day 2 - correlate with the degree of pain patients may experience during dysmenorrhea (Jahangirifara et al., 2018; Willman et al., 1976; Lumsden MA et al., 1983). The standard of care treatment for PDM ranges from non-steroidal anti-inflammatory drugs (NSAIDs) to hormonal contraception (Burnett & Lemyre, 2017). A systematic review from the Cochrane database shows that NSAIDs, including ibuprofen, are significantly superior at treating PDM compared to placebo since they block the production of prostaglandins (OR 4.37, 95% CI 3.76 to 5.09) (Marjoribanks et al., 2015).

However, NSAIDs carry an important risk of side effects, mainly gastrointestinal and neurological (Marjoribanks et al., 2015). Moreover, studies report that 20% to 25% of women are non-responsive to NSAIDs (Proctor et al., 2005). Therefore, there is an unmet medical need for treatment alternatives for those who experience side effects, have contraindications, or are refractory to first-line treatments. Cannabidiol (CBD) has been suggested as a possible alternative, as it inhibits inflammatory cytokine pathways and, like NSAIDs, blocks prostaglandin-triggering enzymes (Dawood, 1988). CBD has also been established as a well-tolerated FDA-approved active pharmaceutical compound used to treat several conditions, including chronic pain. It acts via central and peripheral mechanisms with a well-established and acceptable safety profile (Iffland & Grotenhermen, 2017, Zou & Kumar, 2018).

To our knowledge, this will be the first study to evaluate CBD alone in treating acute menstrual pain in PDM patients, thus addressing a significant gap in the evidence regarding alternative approaches for managing this highly distressing disorder. We aim to conduct a non-inferiority study in females 18 to 40 years of age suffering from moderate to severe PDM to determine whether the use of CBD tablets 100 mg twice daily is non-inferior in reducing menstrual pain, as compared to women receiving ibuprofen, 400 mg twice daily, during the first three days of the cycle, over four consecutive cycles. We hypothesize that CBD will provide a grade of relief of menstrual pain not less than that of ibuprofen.

Materials and Methods

Trial Design

The present study is a phase II, multicenter, randomized, triple-blind, two-arm parallel-group trial comparing CBD vs. ibuprofen. This trial was designed according to the SPIRIT statement (Chan et., 2013) as a non-inferiority trial to evaluate CBD effects on pain relief compared to ibuprofen in women with moderate to severe PDM. This trial will be registered in ClinicalTrials.gov, an International Committee of Medical Journal Editors (ICMJE)-approved public registry.

Study Setting

The study shall be conducted in outpatient clinics at multiple University of Toronto campuses (St. George, Scarborough, and Mississauga) across Ontario, Canada, where homogeneity of the study population can be maintained. The attending gynecologists from the three enrolling campus sites will be instructed to recruit the sample population based on patient inclusion criteria.

The study consists of three phases: screening, treatment, and follow-up visits. The screening phase will last one period (i.e., one menstrual cycle). In this phase, university gynecologists in the enrolling campuses may schedule screening tests on multiple days, as needed. The treatment phase will last four consecutive periods (i.e., four cycles). In this phase, patients will have a remote, monthly clinical consultation and answer the questions regarding the previous cycle (**Figure 1**).

Qualified participants from the three campuses will be randomized in a 1:1 ratio into one of the two treatment groups. The authors anticipate that approximately 300 patients will be screened in the first month before the first treatment period to assess that 108 patients will be randomized. Given that approximately 74,000 students at the University of Toronto (University of Toronto Quick Facts, 2021), of which approximately half (37,000) are females, we can estimate that a pool of at least 34% of these (12,000) may have PDM. If each female student visits the clinic yearly for a gynecologic exam, up to 12,000 per year or 1,000 per month could be screened. This is likely an overestimate; however, even at 30% of this rate, we would meet the target of 300 patients per month.

Data will be collected using the REDCap (Research Electronic Data Capture) platform (Harris et al., 2009, Harris et al., 2019). We will create different questionnaires for study personnel and patients. During the first visit, study personnel will answer the questions with the patient's baseline information and instruct them on how to answer their questionnaires remotely. Patients will have specific questionnaires (e-dairy constructed in REDCap) to collect period times, pain scales, symptoms, side effects, medication usage, and breakthrough medication usage.

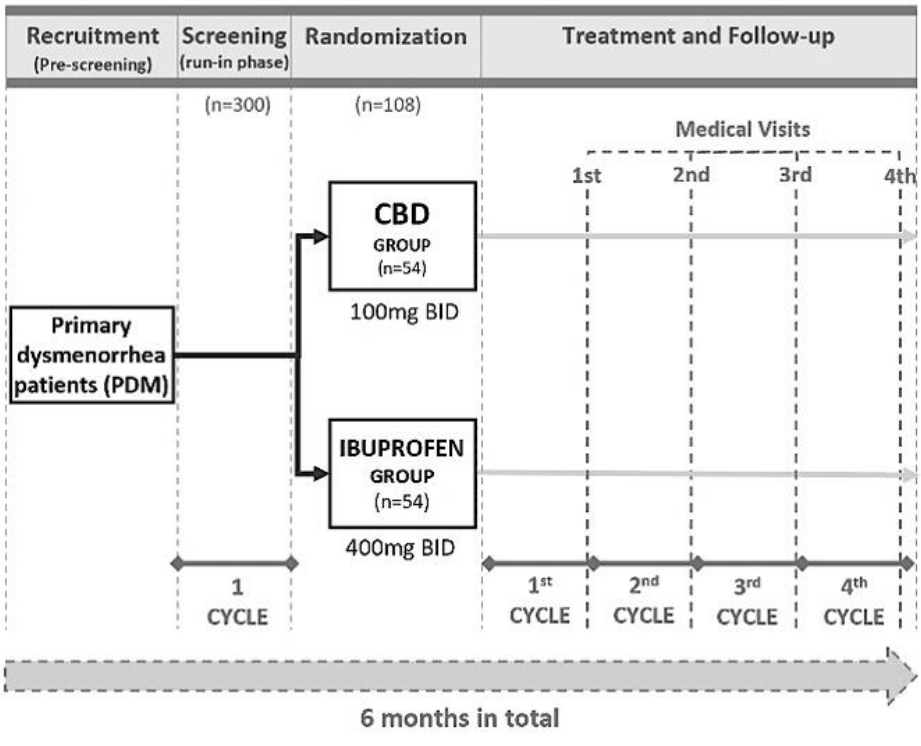

Figure 1. Schematic flow diagram of a non-inferiority study of patients with Primary Dysmenorrhea in a parallel-group design.

Randomization

Each patient will be identified by the study site's unique patient identification code. After the screening and informed consent procedure of enrolling in the trial, each patient is given a screening number (SNR). Eligible patients will be assigned to treatment via RedCap in a 1:1 allocation ratio using random block sizes (4 and 6). The selection of this strategy balances assignment throughout the trial and preserves allocation concealment. No stratification will be used.

Blinding

The study will be triple-blinded. Thus, the patients, research team, and statisticians shall be blinded to the treatment allocation. Study pharmacists will be the only unblinded link in the chain. Blinding will be assessed using the Jame's Blinding Index (James et al., 1996) in the second and fourth menstrual cycles outside the bleeding period. The drug capsules (CBD or ibuprofen) will be identical in size, color, shape, flavor, and daily intake (twice a day) (Bello et al., 2016).

Emergency unblinding will be guaranteed in the event of severe or life-threatening emergencies. The patient will be asked to carry their emergency contact information for the study pharmacists. In addition, the patients will be instructed to use designated emergency departments (ED) from the University of Toronto with available information on the trial. The study pharmacists will be prepared to provide 24/7 support to answer calls and to REDCap. Each situation will be evaluated by a designated independent Data and Safety Monitoring Board (DSMB). Adverse reactions (AR) will be recorded, evaluated, and analyzed by primary investigators and regulatory agents to determine if the signs and symptoms can be associated with the drug.

Participants

Inclusion Criteria:

Patients from 18 to 40 years with PDM with regular menstrual cycles (ranging from 21 to 35 days) and absence of secondary dysmenorrhea. Patients must exhibit moderate to severe pain assessed by the visual analog scale (VAS) pain score ≥ 5.

Exclusion Criteria:

Females with body mass index (BMI) ≥30 kg/m2 or <18 kg/m2, who regularly use other medications, vitamin supplements, or any NSAIDs ≥ 5 days per month or continuous use for the last 60 days and are known non-responders to NSAIDs (1); history of alcohol or drug use, moderate to severe psychiatric disorders, allergy to ibuprofen, CBD, or anticoagulants (2); use of hormonal contraceptives or hormonal intrauterine contraceptive devices (IUCD) within the past three months (4); history of a preexisting condition of secondary dysmenorrhea including the following: Pelvic inflammatory disease (PID), Uterine fibroids, Abnormal pregnancy (miscarriage, ectopic), Infection, tumors, or polyps in the pelvic cavity (5); current breastfeeding and pregnancy (6); previous history of gynecological surgical interventions or scheduled for major surgery during the study period (7).

Recruitment Strategy

A targeted approach will be implemented to recruit participants for this trial. Recruitment will be carried out at the campus clinics of the University of Toronto. Patients will originate from the three cities of the study setting, whose clinic gynecologists will be asked to refer the ones who meet the inclusion criteria. Posters will be placed in common areas of the health centers, clinics, and outside the women's washrooms.

Adherence

Questionnaires will be answered using an e-diary app synchronized with RedCap, and adherence will be monitored continuously. If patients fail to answer the questionnaires, they will be reached by phone. Patients will be provided a Starbucks Gift card (CAD 40) for their participation, for acknowledgment of their time and effort contributed to the study trial. Token gifts will be provided regardless of the continuation of the trial.

Timeline

The subjects will use the e-diary to record the time and date of both study treatment and breakthrough medication intake. They will also use it to fill in pain scales and record symptoms and side effects. The plan and measures of this protocol are presented in **Table 1.**

Interventions

After randomization, the enrolled patients will receive a kit containing B-hCG tests, complementary information about the trial, and instructions to download an app with an e-diary to log their summaries of

Medical Visit	Urine B-hCG	E-diary
Screening	Yes	Training
1st cycle	Yes	Yes
2nd cycle	Yes	Yes
3rd cycle	Yes	Yes
4th cycle	Yes	Yes
Last visit	No	Yes

Table 1. Study timeline includes the plan and measures for each phase.

pain assessments. The e-diary will be an app in which patients can enter data for each assessment. The app will be synchronized with the REDCap database and send reminders for patients (medication intake and questionnaire completion) and reports to the research team.

Patients will be required to perform a quantitative B-hCG blood test before being designated for treatment and require a negative result to continue the study. Patients will be trained to log their pain assessments and take their assigned medication. Regardless of the allocated group, patients will take the study drug twice a day for four consecutive days on each of the four cycles, starting one day before the normal first day of bleeding of their menstrual cycle and after that for three days after their menstrual cycle begins. If they experience inadequate pain relief, participants can take another dose of their assigned medication at intervals of 90 minutes between each dose and not exceeding six capsules per day (2400 mg of ibuprofen and 600 mg of CBD). Patients should record details of all the usage of breakthrough medications (including time of intake, dosage, number of pills/capsules, and route of administration), and other forms of reducing pain methodologies (physical and psychological therapies), in the e-diary.

Patients will be indicated to suspend all painkillers or additional supplements, topical heat/cold pads/therapies, and other topical products intended to provide pain relief approximately two days before and after their menstrual cycle. Patients will be instructed to use the e-diary to log when the capsules were ingested (Time, Date, Number of capsules) for three days of their menstrual cycle and log changes in pain relief. After consumption of the treatment capsules, the patient will fill out the pain relief assessment (TOTPAR), using the e-diary over the first 6 hours for all three days when they are scheduled to take study treatment.

Modification/discontinuation

Suppose the patient has consumed the treatment capsules a day before the typical first day of bleeding of their menstrual cycle, but the cycle has not started in the next two days as expected. They are then required to inform through a phone call to the study site before stopping the treatment. Recruited patients must record every breakthrough medication usage (extra capsule of the assigned medication) in the e-diary.

Outcomes

Primary Outcomes

The study's primary outcome will be pain relief measured using the TOTPAR scale. It assesses the degree of changes in pain relief, ranging from 0 to 4; Grade 0 is defined as no pain relief; Grade 1 is slight pain relief; Grade 2 is moderate pain relief; Grade 3 is good (a lot) pain relief, and Grade 4 complete pain relief after taking the medication.

The patients will be assessed by the TOTPAR scale hourly (1 to 6 hours after medication twice a day) on the first three days of the menstrual cycle over four consecutive cycles, and their results will be analyzed as the overall TOTPAR for each of the groups (CBD and ibuprofen), as shown in **Figure 2**.

Secondary Outcomes

The secondary outcomes will analyze absolute pain, the need for breakthrough medications, quality of life, and the reporting of severe or life-threatening clinical adverse events. Patients will be instructed to record every time they take an extra dose of the study medication, and we will register the need (yes/no), the total amount, and the interval between doses. A quality of life (QoL) assessment will be performed after using the study medication. Each patient will be given a WHOQOL-pain (Mason et al., 2009) questionnaire to evaluate their life quality during every month of the study. All site-reported adverse clinical event cases will be individually assessed and adjudicated by an independent Clinical Event Adjudication Committee (CEAC) based on a predetermined charter of expected CBD and NSAID side effects following the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (Dueck et al., 2015).

Data Management

Data Monitoring

We will use electronic case report forms to manage data through REDCap software for electronic data capture to create, maintain, transmit, and monitor data. The independent Safety Data Monitoring Committee will consist of a statistician and one obstetrician-gynecologist (OB-GYN) experienced in clinical trial procedures, both not directly involved in the study or with competing interests.

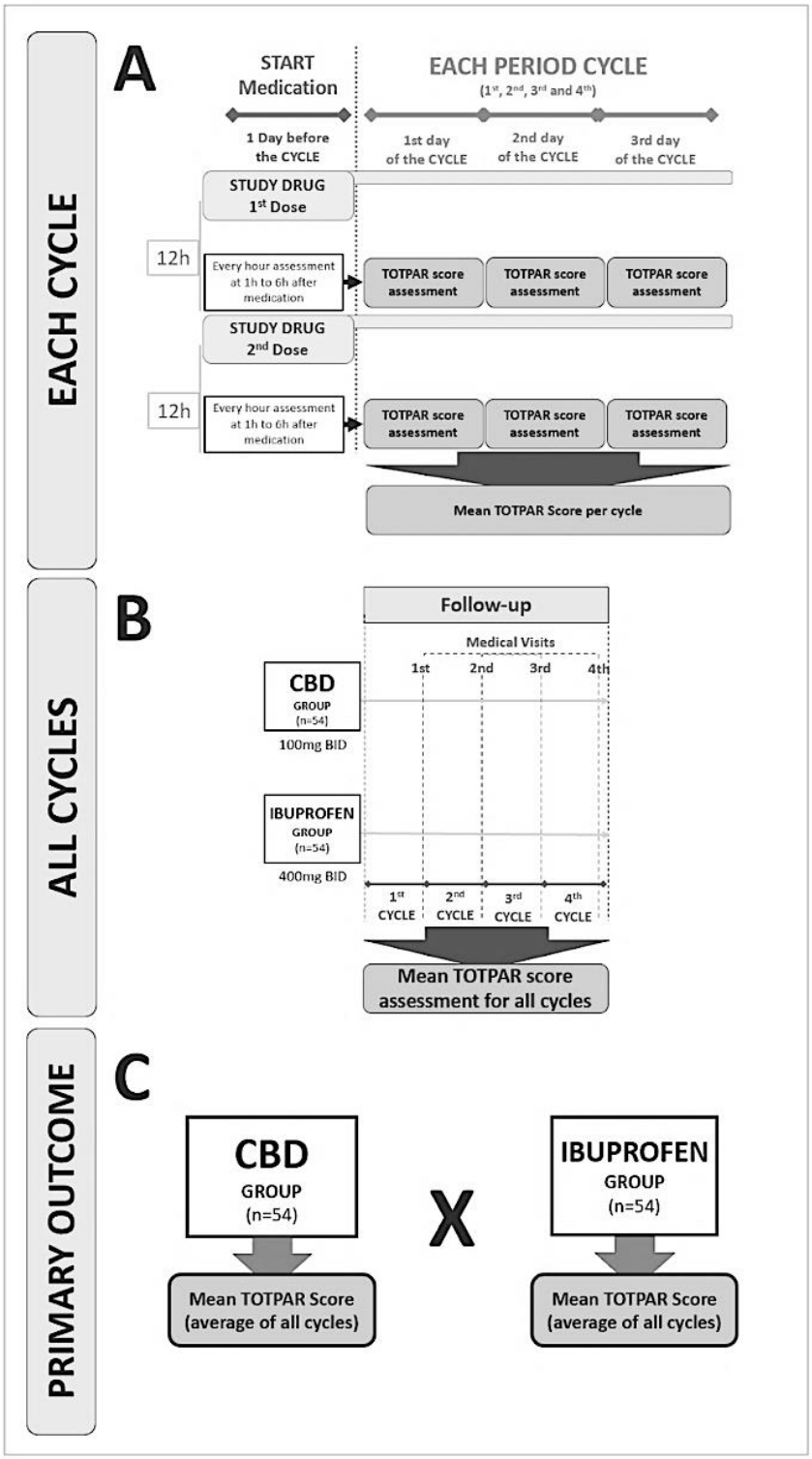

Figure 2. Primary outcome analysis: TOTPAR scale assessment for each menstrual cycle (A); TOTPAR scale assessment of all cycles (B); and TOTPAR scale assessment of CBD vs. Ibuprofen (C). Abbreviations: CBD = cannabidiol; TOTPAR = total pain relief.

Interim Analysis

The interventions have anticipated low toxicity and the disease has a stable course. Therefore, we do not plan on performing an interim analysis since it could increase type I and II errors, impact power and reduce clinical significance.

Sample Size Calculation

For sample size calculation and non-inferiority margin purposes, the alternative hypothesis is that CBD is non-inferior to ibuprofen in acute pain relief. The threshold for the non-inferiority margin (M) of ibuprofen will be the lower bound of the 95% CI of the least square mean difference between treatment groups. The estimated effect in pain reduction is 20% of the expected pain relief provided by ibuprofen, measured by a TOTPAR of 16.49, as described by Yu et al. (2014), with a significance level of 0.05. We propose a sample size of 108 subjects, with 54 patients per treatment arm. Calculations considered a 15% non-inferiority margin, alpha of 5%, a beta of 20%, and a statistical power of 80%, the mean TOTPAR of 16.49 for ibuprofen and 14.02 for CBD, resulting in a required sample of 86 subjects to achieve significance. A predicted dropout rate of 30% was used to adjust the sample size to the final 108 subjects (Connor, 1987, Farrington, 1995, Musonda et al., 2006, and Rosner, 2010). These results were obtained using an open-access calculator (http://powerandsamplesize.com/).

Statistical Analysis for primary and secondary outcomes

The primary outcome will be assessed by comparing the mean pain relief of each treatment arm. Based on the sample size and the Central Limit Theorem, normal distribution will be assumed and visually inspected using a histogram. The primary outcome will be analyzed using a parametric one-sided, unpaired t-test. We will evaluate both intention to treat and per protocol, as appropriate for a non-inferiority trial, and evaluate the robustness of the results using sensitivity analysis.

For secondary outcomes, the mean pain VAS will be compared between groups using a 2-sided t-test and may be used for subgroup analyses of the primary endpoint. A Fisher's exact independent test will be used for the binary outcomes of breakthrough medication use. We will describe the mean dose used for each assigned medication and the mean time between each dose. The mean WHOQOL score for each domain (physical, psychological, environmental, social) will be calculated for cycles 2 to 4 and compared between groups using a 2-sided t-test.

All tests will be performed using a 0.05 significance level. However, the study is not powered to detect a difference in secondary outcomes; the events will be assessed by a clinical judgment for any concerning patterns.

Data will be analyzed using Stata 17 Software (StataCorp, 2021).

Missing Data

In this study, we might have missing data for the reasons that follow: participants may drop out before the study completion, may refuse the assigned treatment after allocation, not provide relevant data by failing to complete diaries or questionnaires assigned to them in this study (such as the TOTPAR). Defined by the study design, an intention to treat (ITT) and per-protocol (PP) analysis will be used. Finally, we will use the Complete Case Analysis (CCA) for missing data points.

Discussion

This study is the first randomized clinical trial aiming to treat PDM using CBD alone, without any additional treatment or supplementations. This trial intends to test whether CBD can have analgesic effects non-inferior to the current standard of care NSAIDs.

While NSAIDs can have troubling side effects, the side effects of CBD are rare and mild when consumed in low doses. There is no description of side effects with a CBD acute oral use dosage of 15 to 160mg/day (Bergamaschi et al., 2011). Moreover, at higher doses, up to 600 mg (daily), it does not interfere with psychological or motor functions, memory, learning, heart rate, or blood pressure, which are the main possible side effects of a high dose of CBD (Zuardi, 2008). Therefore, the low therapeutic dose chosen is expected to provide a strong analgesic effect while diminishing the probability of adverse effects.

It is accepted that there will be limitations. The taboo over using a new drug is reduced by selecting a population where CBD is culturally accepted. Due to the strict exclusion criteria and multiple assessments implied by the study design, it was necessary to opt for an electronic device that would improve the subject's adherence and maximize data accuracy. Furthermore, administering the treatment a day before the menstrual cycle will aid in preventing false-negative results in the statistical analysis, given the delayed action peak of the drug.

Therefore, this trial aims to provide much-needed evidence that oral CBD alone is as safe and effective as ibuprofen and presents as an interesting alternative to treat pain in women living with PDM who do not

respond to NSAIDs or who have unacceptable side effects related to them.

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