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The effects of cannabidiol isolate on menstrual-related symptoms

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The Effects of Cannabidiol Isolate on Menstrual-Related Symptoms

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Abstract

The current study aimed to examine the potential effects of CBD isolate for alleviating menstrual-related symptoms (MRS). Participants (N = 33, M_{AGE} = 20.50, M_{BMI} = 23.02) were assigned randomly to two open-label dosing groups (160mg, n = 17; 320mg, n = 16) and completed monthly surveys for four months that included MRS-related measures. We examined differences in MRS and related outcomes between baseline and three months of CBD administration. Results revealed reductions in MRS, irritability, anxiety, global impression, stress, and subjective severity scores with a small effect when comparing baseline to all three months of CBD administration. Findings suggest that CBD may have potential for treating MRS. Further research is warranted examining the potential to optimize CBD administration for reducing MRS (i.e., terpenes, routes of administration, time of administration).

Keywords: menstruation, menstrual-related symptoms, cannabidiol, intervention, treatment

The Effects of Cannabidiol Isolate on Menstrual-related Symptoms

Menstrual-Related Symptoms

Most menstruating individuals experience some form of discomfort or dysphoria in the days or weeks before menstruation (Yonkers et al., 2008). Approximately 75% of those who menstruate experience unpleasant menstrual-related symptoms (MRS; Wakil et al., 2012). MRS, including but not limited to premenstrual syndrome (PMS) symptoms, are characterized by both physical (e.g., cramps, headache, breast tenderness) and psychological (e.g., irritability, tension, depressed mood) experiences (Yonkers et al., 2008). Findings from prospective and retrospective studies suggest that 5-8% of individuals who experience menstrual cycles have moderate to severe symptoms (though some studies suggest this is an underestimation— e.g., Direkvand-Moghadam et al., 2014; Halbreich et al., 2003) and up to 20% of fertile-aged individuals have clinically relevant premenstrual complaints (Borenstein et al., 2003).

The menstrual cycle (MC) occurs in five phases: menstrual (days one-five), follicular (days six-12), ovulatory (days 13-16), luteal (day 17 to the premenstrual phase), and premenstrual (five days prior to menstrual bleeding; Evans et al., 1998; Johannes et al., 1995; Pastor & Evans, 2003); MRS are most often experienced in the menstrual and premenstrual phases. Premenstrual symptoms, a sub-set of MRS that present in approximately 20-40% of reproductive aged individuals (Mischell, 2005), often occur cyclically beginning in the luteal phase and subside quickly after menstruation onset (Strine et al., 2005). Symptom expression among individuals varies between a few days and two weeks; symptoms often worsen approximately 6 days before and peak at 2 days prior to menstruation (Pearlstein et al., 2005; Meaden et al., 2005). Individuals who

experience severe PMS symptoms that include at least one disabling affective symptom (e.g., affective lability, irritability, anxiety) might be diagnosed with premenstrual dysphoric disorder (PMDD), which occurs in approximately 3-9% (24 to 72 million) of menstruating individuals (Halbreich et al., 2003). PMDD is the psychologically dominated form of PMS, characterized by depressed mood, anxiety, irritability, anger, and insomnia all attributable to the menstrual cycle (Halbreich et al., 2003; Indusekhar et al., 2007). Despite the widespread impact of PMDD and PMS, up to 89% of those who likely suffer from PMDD may go undiagnosed (Halbreich et al., 2003) and it is estimated that less than half of those with severe PMS seek medical support or intervention (Hylan et al., 1999). Because MRS are often conflated with other medical conditions and disorders (e.g., pain, depression), PMS and PMDD are difficult to identify and diagnose. Some individuals may experience psychological symptoms as a result of disabling physical symptoms (and/or vice versa) making diagnosis even more challenging.

Though MRS are often mild, they can be severe enough to disrupt daily life; one in 3 menstruating individuals halt typical daily activities because of menstrual symptoms (Shoep et al., 2019). Moderate to severe MRS can be psychologically and physically disabling in areas ranging from family and personal relationships to work productivity and social activities (Freeman, 2005). Individuals with severe MRS may experience symptoms for up to 2,800 days (~7.7 years) across their reproductive age span, which can have a substantial impact on various domains of their lives (Halbreich et al., 2003). Some consequences of MRS include absenteeism, lost wages, lowered productivity, adverse effects on relationships, and diminished quality of life (Borenstein et al., 2003; Borenstein et al., 2007).

MRS and Clinical Relevance

The presence of MRS have been studied extensively; however, more clinical research is necessary, not only because of its impact on everyday life, relationships, and economic losses (Halbreich et al., 2003), but also because of the association between MRS and psychiatric symptomatology and diagnosis (Gonda et al., 2008). Though symptoms vary considerably across individuals (Steiner & Born, 2000), the collective impact of psychological distress from MRS may pose important public health implications. Strine and colleagues (2005) found that individuals who experience MRS are 1.7 to 3.0 times more likely to report insomnia or sleepiness, recurrent pain, sadness, nervousness, restlessness, hopelessness, worthlessness, and that everything was "an effort"; these symptoms often resulted in impaired quality of life and inability to maintain engagement in everyday activities (Strine et al., 2005). Additionally, behavioral responses during menstruation, such as reduced social engagement, may also contribute to feelings of isolation and depression (van Iersel et al., 2016).

Ovarian hormonal changes that occur during the premenstrual phase of the menstrual cycle may establish a neuro-modulatory influence that contributes to the onset and maintenance of maladaptive or clinical anxiety among those who menstruate (Nillni et al., 2011). These hormonal changes that occur throughout the menstrual cycle are associated with changes in affect and increases in symptoms that are associated with a multitude of mental health conditions (Brier et al., 1986; Freeman et al., 2003; Gonda et al., 2008; Kaspi et al., 1994; Kornstein et al., 2008). The association between hormonal influence and mental health outcomes is also consistent with findings that show treatment

through ovarian suppression with leuprolide reduced symptoms among those with premenstrual syndrome (Schmidt et al., 1998).

More specifically, the premenstrual phase is associated with exacerbations of mood and anxiety disorders such as major depression (Kornstein et al., 2008), panic disorder (Breier et al., 1986; Cook et al., 1990; Kaspi et al., 1994), and bipolar disorder (e.g., Rasgon et al., 2003). Typically, symptoms that characterize these disorders intensify during the late luteal phase, when progesterone and estradiol are declining, and during the early follicular phase, when levels of progesterone and estradiol are both at their lowest levels (Hendrick et al., 1996). Those who experience PMS have a higher prevalence of major depressive disorder (MDD) and anxiety disorders and greater risk of subsequent development of incidental affective disorders than do individuals without PMS (Rubinow et al., 1998). Other disorders that are associated with certain phases of the menstrual cycle include eating disorders (e.g., Lester et al., 2003) and substance use disorders (e.g., Allen, 1996; Evans et al., 2002). Additionally, findings have suggested an association between the premenstrual phase and psychiatric admissions (Jang & Elfenbein, 2019) and that individuals may be at greater risk of suicide attempts and completed suicides during the menstrual phase (Saunders & Hawton, 2006).

Currently Available Treatments

Though MRS are prevalent and, often, debilitating, effective remedies for managing symptoms are scarce. Managing symptoms associated with menstruation is complex given the variability in symptoms across individuals who menstruate. As a result, management of MRS is often frustrating for both patients and health-care providers (Dickerson et al., 2003). Existing interventions range from lifestyle

modifications to hormonal treatments and prescription medications that aim to alleviate symptoms and reduce their impact on everyday activities (Dickerson et al., 2003). Those with mild symptoms might effectively manage symptoms through lifestyle changes, including healthy diet, sodium and caffeine restriction, exercise, and stress reduction (Dickerson et al., 2003) or through of use over-the-counter (OTC) pain medications (OTC; ibuprofen, naproxen) or behavioral remedies (e.g., heating pad). For individuals who experience more severe symptoms, lifestyle changes and OTC medications are often ineffective (Dickerson et al., 2003).

Most available intervention strategies that have been shown efficacious in treating MRS have largely focused on physical symptoms. There is a relative lack of clinical research (and potential intervention strategies) aimed at improving psychological MRS. Clinically meaningful PMS or PMDD, which is primarily characterized by psychological symptoms, are most often treated with pharmacotherapy (e.g., Selective Serotonin Reuptake Inhibitor; SSRI) or hormonal interventions (e.g., birth control); however, these interventions have only shown clinically meaningful improvement in approximately 60% of those who engage with the interventions (Pearlstein and Steiner, 2008). Though SSRIs have shown some improvement in treating MRS, side effects often occur with SSRI use. Common side effects of SSRIs include insomnia, drowsiness, fatigue, nausea, nervousness, headache, mild tremor, and sexual dysfunction (ACOG, 2000; Dimmock et al., 2000).

Hormonal strategies have also been used to treat PMS and PMDD; these interventions include long-acting gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide, and combined oral contraceptives (COCs; i.e., birth control pill), or other

hormonal birth control methods. Leuprolide and birth control methods may be effective in alleviating symptoms (affective lability, anxiety), but there are also a multitude of side effects from these treatments. Leuprolide, which functionally results in medical menopause, is associated with side effects including hot flashes, night sweats, and vaginal dryness (Wyatt et al., 2004), and potentially puts individuals at risk for osteoporosis (Cunningham et al., 2009). Birth control has been found to induce or worsen feelings of dysphoria (Bhatia & Bhatia, 2002) and is associated with a greater likelihood of adverse mood symptoms (Jungheim et al. 2009). Birth control is also implicated with increased risk of endometrial cancer, coronary heart disease, breast cancer, stroke, and pulmonary embolism (Rossouw et al. 2002).

Though there are treatments to alleviate specific acute symptoms (e.g., cramps, headaches, breast sensitivity), there are no effective treatments to date that target physical and psychological symptoms simultaneously and that do not introduce side effects and/or increase medically-relevant risk factors. Given the lack of adequate treatments to alleviate symptoms, many individuals self-medicate. Self-medication theory (SMT) suggests that individuals experiencing periods of greater negative affect or physical symptoms may use substances to cope with those experiences (Khantzian, 1997; Joyce et al., 2019). Indeed, findings have consistently supported that those who experience PMS are more likely to drink alcohol in effort to cope with symptoms, more specifically, negative mood (Carroll et al., 2015; Epstein et al., 2006; Strine et al., 2005). Prior research has also suggested that nicotine use increases during the premenstrual phase of the menstrual cycle (Joyce et al., 2019).

Recent literature also suggests that some individuals attempt to alleviate MRS by using cannabis and report having expectations that cannabis can improve MRS (Hanzal et al., 2019; Slavin et al., 2017). Slavin and colleagues (2017) found that individuals reported expectancies that cannabis would alleviate all symptoms associated with PMS/PMDD except for overeating/food cravings. Specifically, participants reported that they believed cannabis would help treat irritability, labile affect, depressive moods, anxiety, and sleep disturbances more so than physical symptoms including breast tenderness and bloating (Slavin et al., 2017). Consistent with SMT, individuals with expectancies related to positive MRS outcomes associated with cannabis use also reported greater MRS and greater monthly cannabis use (Slavin et al., 2017).

A recent study examined whether increases in depressed mood and coping motives would predict increased pre-menstrual and menstrual cannabis use among naturally cycling cannabis users with and without retrospectively identified PMDD (via structured clinical interview) and prospectively identified PMDD (via elevated pre-menstrual depressed mood; $N = 69$; $M_{age} = 29.25$, $SD_{age} = 5.66$). Joyce and colleagues (2021) employed electronic daily diary methods and validated menstrual phase by using salivary progesterone concentrations across 32 days. Findings showed that coping motives were associated with heightened pre-menstrual and menstrual phase cannabis use in those with retrospectively identified PMDD and depressed mood was associated with increased menstrual-phase cannabis use in those with retrospectively/prospectively identified PMDD. Further, prospectively identified PMDD meaningfully moderated the relation between depressed mood and menstrual-phase cannabis use quantity. In those with prospectively identified PMDD, positive mood and enhancement motives were

associated with decreased cannabis use during the follicular/ovulatory phases. Individuals with retrospectively identified PMDD also displayed greater overall cannabis use quantity (measured by number of standard joints; $M = 3.44$, $SD = 2.84$) compared to individuals without retrospectively identified PMDD ($M = 1.85$, $SD = 1.82$; $p = 0.008$; Joyce et al., 2021).

Given the prevalence and salience of MRS and the relative paucity of remedy options for the whole range of symptoms, consideration of novel intervention strategies is warranted. One intervention strategy with potential to impact a wide range of symptoms that overlap with MRS (including irritability, depressive moods, anxiety, pain, and sleep disturbances) is cannabis use, specifically cannabidiol (CBD; Russo et al. 2007; Russo & Hohmann 2013; Slavin et al., 2017).

Cannabis and MRS

Cannabis has been shown to have therapeutic effects on physical (Reiman et al., 2017) and psychological (Solowij et al., 2018) experiences. Phytocannabinoids (cannabinoids that occur naturally in the cannabis plant) found in cannabis work on the endocannabinoid system, which consists of a series of neuromodulatory lipids and receptors located throughout the central and peripheral nervous systems that accept endogenous cannabinoids (anandamide, 2-arachidonoylglycerol) and phytocannabinoids. The two most abundant (in the plant) and well-researched phytocannabinoids are delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD; Babson et al., 2017; Haney, 2022).

Recent literature has examined the potential health benefits of non-intoxicating or minimally psychoactive extracts and constituents of the cannabis plant (Lopez et al., 2020). Though THC has high-inducing effects, in which users often feel euphoric, CBD

does not elicit the same high-inducing or impairing effects that are observed with THC (Maroon and Bost, 2018). Hemp-derived CBD (cannabis with less than 0.3% THC content by dry weight) can be consumed as whole plant or as a CBD isolate; whole-plant hemp-derived CBD includes a complex phytochemical matrix from the plant while CBD isolate has no other cannabinoid constituents present (Marinotti & Sarill, 2020). In addition to whole-plant and isolate, researchers and pharmaceutical companies can develop targeted formulations of CBD combined with terpenes and/or flavonoids in effort to achieve specific outcomes (e.g., improved anxiety versus improved sleep).

CBD (whole plant, isolate, and targeted formulations) has been demonstrated to yield a range of possible therapeutic effects (Schier et al., 2012); more specifically, CBD has demonstrated various beneficial health outcomes such as mood regulating, neuroprotective, analgesic, anti-inflammatory, anxiolytic, and immunomodulatory effects (Schultes 1969; Campos et al. 2016; Hillard 2000). Chronic pain is one of the most often cited reasons that patients are accessing medicinal cannabis in states where it is available (Sexton et al., 2016). More specifically, approximately 36% of medical cannabis users reported using cannabis for headaches or migraines; these users reported an average 3.6-point decrease (on a 10-point scale) in headache severity after cannabis use (Sexton et al., 2016). Although the effectiveness of CBD- isolate for pain management has not been well assessed clinically, nabiximols (cannabis extract containing THC and CBD) have shown promising results in symptomatic pain management (Boyaji et al., 2020; Überall, 2020). An analysis including seven trials of nabiximols, and one trial of smoked whole-plant cannabis demonstrated that the plant-derived cannabinoids were 40% more likely to reduce pain than the placebo (Andreae et al., 2015).

CBD has also shown anxiolytic effects in both animal and human studies (Zuardi et al., 1993; Zuardi et al., 2006). Zhornitsky and Potvin (2012) suggest that high-doses of CBD (150-600mg/daily) may decrease anxiety and increase mental sedation in healthy individuals; clinical trials have demonstrated that high-dose CBD may be useful for the treatment of social anxiety disorder as well as insomnia. CBD's anxiolytic effects are similar to those of approved drugs to treat anxiety (Resstel et al., 2009). In a clinical trial with individuals diagnosed with social anxiety disorder, each participant received either a single dose of 600 mg of CBD or a placebo before completing a simulated public speaking test; CBD was associated with a greater decrease in anxiety compared to the placebo group (Bergamaschi et al., 2011).

The endocannabinoid system has also been implicated for its role in sleep, and more specifically, the effects that cannabis may have on sleep latency (Jang & Elfenbein, 2019). Clinical evidence has demonstrated that both adults and adolescents may use cannabis to cope with sleep disturbances (Babson & Bonn-Miller, 2014). Varying doses of CBD have been shown to have differential effects on wakefulness; low-doses of CBD have demonstrated a stimulating effect, while high-doses have shown a sedating effect (Babson et al., 2017). In a study among individuals with insomnia, findings showed that ingestion of 160mg daily of CBD increased total sleep time and decreased the frequency of arousals during the night (Carlini & Cuhna, 1981).

Another notable benefit of cannabis as a form of treatment is safety (Shannon et al., 2019) compared to other currently available treatments for MRS that have the potential for abuse, overdose, and adverse side effects (e.g., OTC pain medications, SSRIs; Reiman et al., 2017). According to exhaustive reviews, both healthy individuals

and clinical patients with different conditions did not experience significant adverse effects to acute or chronic administration of CBD by various routes (Bergamaschi et al., 2011; Iffland & Grotenhermen, 2017).

Although CBD has been shown to have a range of health benefits, there is a relative dearth of human clinical data on its potential to affect a variety of health outcomes (Lopez et al., 2020). Given the considerable overlap in symptoms impacted positively by CBD and MRS (e.g., anxiety, sleep disturbance, migraine) and the relative lack of side-effects associated with CBD, it is reasonable to consider that CBD may be a viable option for MRS intervention (Baron, 2018; Carlini & Cunha, 1981; Shannon et al., 2019).

Current Study

Although research has suggested cannabis as a potential alternative treatment for MRS that has fewer side effects compared to currently available treatments (Grotenhermen & Russo, 2002; Slavin et al., 2017), further research is needed to examine its efficacy. The current study aims to examine the potential effects of orally ingested CBD isolate soft-gels on physical and/or psychological MRS. Researchers assigned randomly participants to consume 160mg or 320mg doses of hemp-derived pure CBD isolate (containing no other cannabinoids or cannabinoid-related constituents) to be taken daily for five consecutive days each month beginning the first day that MRS symptoms are experienced. Primary health outcomes of interest include MRS, anxiety, stress, sleep quality, and mood, as well as exploratory health outcomes including alcohol use, depression, and irritability.

Methods

Participants

Participants included (N = 33; M_{AGE} = 20.50, SD_{AGE} = 2.63; M_{BMI} = 23.02, SD_{BMI} = 2.68) individuals who self-reported experiencing a normal menstrual period (occurring every 21-38 days and lasting between 4-8 days; Creinin et al., 2004), were willing to track their menstrual cycle systematically, and experienced moderate-to-severe MRS or are diagnosed currently with PMDD (M_{MRSQ} = 54.85, SD_{MRSQ} = 12.02, *range* = 34-87; *Diagnosed with PMDD* = 0). Individuals who self-reported using cannabis or cannabis-containing product within 30 days of screening, trying to get pregnant, having a past suicide attempt or current suicidal plan in the past year, having a BMI of underweight (18kg/m^2 and below) or obese (30kg/m^2 and above), or having a DSM-5 diagnosis (e.g., current psychotic disorder) or significant disease or disorder (e.g., epilepsy) that would interfere with the study treatment were excluded from the study.

Materials

Screener Measures

Demographics. Demographics consisted of a series of questions regarding age, ethnicity, and questions related to menstrual symptom experience (e.g., birth control usage, menstrual-related health conditions).

Eligibility Questionnaire. A checklist of eligibility criteria included Yes/No statements that participants endorsed or denied.

Menstrual-Related Symptom Questionnaire. The Menstrual-Related Symptom Questionnaire is a 26-item measure adapted from the Menstrual-Symptom Questionnaire (Chesney & Tasto, 1975) containing common physiological and psychological symptoms

that individuals may experience because of their menstrual cycle (Ferretti et al., in press). Respondents report the severity in which they experience each symptom on a four-point Likert scale (1 = *none* to 4 = *severe*). Scores can range from 26 to 104. Internal consistency for this sample is good (Cronbach's α range = 0.77 - 0.89).

Brief Irritability Test (BITe). The BITe is a 5-item self-report measure to evaluate irritability symptoms over the past two weeks (Holtzman et al., 2015). Each item is measured on a six-point Likert scale (1 = *never* to 6 = *always*). A higher total score indicates greater irritability, and scores can range from 5 to 30. All five items displayed minimal conceptual overlap with related constructs (e.g., depression, anger; Holtzman et al., 2015). Internal consistency for this sample is good (Cronbach's α range = 0.83 - 0.90).

Drug Abuse Screening Test (DAST). The DAST is a 28-item self-report measure used to provide a brief clinical screening for examining the extent of drug use involvement. Questions are provided in Yes/No format. A score of 1 on each item response indicates drug use while a score of 0 does not. The internal consistency reliability estimate was a .92, and a factor analysis of item intercorrelations suggested a unidimensional scale (Skinner, 1982). Using a cutoff score of 6 has been found to provide excellent sensitivity for identifying patients with substance use disorders. Internal consistency for this sample is sub-optimal (Cronbach's α = 0.61).

Alcohol Use Disorders Identification Test (AUDIT). The AUDIT is a 10-item screening tool to evaluate for alcohol consumption, drinking-behaviors, and alcohol-related problems (Saunders et al., 1993). A score of '8' or more is characterized as hazardous or harmful alcohol use. Item responses range are measured on a Likert scale (0

= *never* to 4 = *daily or almost daily*), and scores can range from 0 to 40. Internal consistency for this sample is acceptable (Cronbach's α range = 0.68 - 0.83).

Depression, Anxiety, and Stress Scale-21 (DASS-21). The DASS-21 is a 21-item self-report instrument used for measuring depression, anxiety, and tension/stress in the past week. Item Responses are measured on a four-point Likert scale (0 = *did not apply to me at all* to 3 = *applied to me very much or most of the time*). Higher scores indicate higher severity levels of depression, anxiety, and stress; scores can range from 0 to 42. The DASS-21 is a useful tool for screening both clinical and subclinical threshold levels of these emotional states (Lovibond & Lovibond, 1995). Internal consistency for this sample is good (Cronbach's α range = 0.80 - 0.93).

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a 9-item questionnaire that provides an index of sleep quality through a one-month interval of time. Participants answer open-ended questions that are scored based on categories and questions on a 4-point Likert-scale (0 = *very good* to 3 = *very bad*). Sleep pattern indices can be calculated separately or summed to provide a global sleep quality score. Global scores range from 0 to 21 with higher scores indicating worse sleep quality (Buysse et al., 1989). The PSQI is a psychometrically sound measure for use across a variety of clinical and non-clinical populations (Buysse et al., 1989).

Premenstrual Dysphoric Disorder (PMDD) DSM-5 Criteria. Diagnostic criteria for individuals with PMDD are found in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5; American Psychiatric Association, 2013). Individuals endorsed or denied 11 symptoms that are included in the criteria of PMDD.

Columbia Suicide Severity Rating Scale (CSSRS) 4-5. The CSSR is a measure used to assess suicidal risk. The current study only included item 4 "Have you thought about a method of killing yourself but do not intend to act on it" and item 5 "Have you started to work out or worked out details of how to kill yourself? Do you intend to carry out this plan?"

Monthly Survey Measures

Visual Analogue Mood Scale (VAMS). We included one item of the 16-item VAMS. Participants are asked to indicate a point on a straight line placed between two words that describe opposite mood states (happy/positive or sad/negative for this study; Luria, 1975). The VAMS is considered a valid measure and high test-retest reliability was demonstrated both across and within patients (Luria, 1975).

Global Impression of Change. A 7-point scale was used to capture participants' beliefs about the global improvement of their MRS since enrolling in the study.

Menstrual Demographics. Menstrual demographics consisted of questions related to menstrual symptom experience (e.g., birth control usage, menstrual cycle tracking).

Menstrual-Related Symptoms Questionnaire. See description above.

Depression, Anxiety, and Stress Scale-21 (DASS-21). See description above.

Brief Irritability Test (BITe). See description above.

Pittsburgh Sleep Quality Index (PSQI). See description above.

Alcohol Use Disorders Identification Test (AUDIT). See description above.

Drug

CBD Isolate. CBD isolate (extracted and purified from whole-plant hemp) was used for this study in effort to isolate the effects of CBD in the absence of other cannabis plant constituents. CBD isolate was provided in the form of 20mg soft-gel capsules. The CBD was suspended in MCT (medium-chain triglycerides) oil to promote bioavailability of CBD.

Procedures

Potential participants were contacted via bulk email and asked to complete an electronic screener to determine study eligibility through QuestionPro. If at any point during the screener individuals endorsed a question that would exclude them from the study, then the survey truncated. Those who meet inclusion criteria were contacted and invited to join the study. Individuals that were interested in enrolling were assigned randomly to one of 2 open-label study groups (160mg, n = 17; 320mg, n = 16) and attended a virtual screening session that included informed consent procedures via Zoom. During informed consent, a research assistant re-screened for eligibility criteria. All participants met criteria at this time.

Participants completed monthly electronic surveys related to MRS for one baseline month. If participants provided at least 80% of requested data for the baseline month, they were provided with a 3-month supply of CBD isolate. Participants were asked to continue completing the monthly surveys related to MRS throughout the 3-month period during which they took the provided CBD. Starting the first day that participants believed they were experiencing symptoms each month, they began taking their assigned dose daily for five consecutive days.

Data Analysis Plan

Data were analyzed using SPSS (Version 28.0). Descriptive statistics were used to characterize participants' age, race, birth control use, diagnoses that impact the MC (i.e., PMDD), menstrual tracking, and health outcomes throughout the study (see Tables 3, 4). Descriptive statistics were used to summarize health outcomes in the screener and bivariate correlations were conducted to examine relations between study outcomes throughout the study (see Tables 1, 2). All internal consistency data are presented as ranges to reflect internal consistency for all time points for which we administered the measures.

Researchers examined whether various health outcomes differed from baseline to the three different intervention months and between dosing conditions. A series of mixed 2x4 ANOVAs were conducted to examine potential changes in all health-related outcomes from baseline to months one, two, and three of CBD administration between dosing conditions (160mg and 320mg).

Results

Screener Analyses

Descriptive statistics are presented in various tables (see Tables 1, 3, 4, 5). A series of correlations were conducted to examine relations between study outcome variables (see Table 2).

Monthly Analyses

We conducted a series of mixed 2 (condition) x 4 (month) ANOVAs to examine potential changes in health-related outcomes from baseline to all three months of CBD administration between dosing groups (160mg and 320mg).

MRS

A 2x4 mixed ANOVA revealed a meaningful main effect of time on MRSQ scores (Greenhouse-Geisser Adjusted; $F(2.43, 75.39) = 17.42$, $p < .001$, $\eta_p^2 = 0.36$, observed power = 1.00). Regardless of dosing condition, participants yielded meaningfully higher baseline MRSQ scores ($M = 51.51$, $SD = 1.78$) compared to months one ($M = 45.04$, $SD = 1.46$), two ($M = 41.03$, $SD = 1.04$), and three ($M = 41.87$, $SD = 1.24$) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time (Greenhouse-Geisser Adjusted; $F(2.43, 75.39) = 0.83$, $p = 0.48$, $\eta_p^2 = 0.03$, observed power = 0.20) or main effect of dosing condition ($F(1, 31) = .01$, $p = 0.92$, $\eta_p^2 = 0.00$, observed power = .05) on MRSQ scores.

A 2x4 mixed ANOVA revealed a meaningful main effect of time on physiological MRSQ scores (Greenhouse-Geisser Adjusted; $F(2.15, 66.66) = 11.66$, $p < .001$, $\eta_p^2 = 0.27$, observed power =1.00). Participants yielded meaningfully higher baseline physiological MRSQ scores ($M = 25.79$, $SD = 1.03$) compared to months one ($M = 22.87$, $SD = 0.67$), two ($M = 21.24$, $SD = 0.67$), and three ($M = 21.53$, $SD = 0.63$) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time (Greenhouse-Geisser Adjusted; $F(2.15, 66.66) = 0.15$, $p = 0.87$, $\eta_p^2 = 0.10$, observed power = 0.07) or main effect of dosing condition ($F(1, 31) = .02$, $p = 0.92$, $\eta_p^2 = 0.02$, observed power = 0.13) on physiological MRSQ scores.

A 2x4 mixed ANOVA revealed a meaningful main effect of time on psychological MRSQ scores ($F(3, 93) = 12.13$, $p < .001$, $\eta_p^2 = 0.28$, observed power =1.00). Participants yielded meaningfully higher baseline psychological MRSQ scores ($M = 20.97$, $SD = 0.85$) compared to months one ($M = 18.48$, $SD = 0.94$), two ($M =$

16.11, *SD* = 0.49), and three (*M* = 16.67, *SD* = 0.73) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time ($F(3, 93) = 1.68$, $p = 0.18$, $\eta_p^2 = 0.05$, observed power = 0.43) or main effect of dosing condition ($F(1, 31) = 1.46$, $p = 0.24$, $\eta_p^2 = 0.05$, observed power = 0.22) on psychological MRSQ scores.

A 2x4 mixed ANOVA revealed a meaningful main effect of time on appetite MRSQ scores ($F(3, 93) = 11.51$, $p < .01$, $\eta_p^2 = 0.27$, observed power = 0.91). Participants yielded meaningfully higher baseline appetite MRSQ scores (*M* = 4.75, *SD* = 0.30) compared to months one (*M* = 3.69, *SD* = 0.23), two (*M* = 3.70, *SD* = 0.22), and three (*M* = 3.67, *SD* = 0.22) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time ($F(3, 93) = 1.39$, $p = 0.25$, $\eta_p^2 = 0.04$, observed power = 0.36) or main effect of dosing condition ($F(1, 31) = .24$, $p = 0.63$, $\eta_p^2 = 0.01$, observed power = .08) on appetite MRSQ scores.

A 2x4 mixed ANOVA revealed a meaningful main effect of time on global impression of change scores ($F(3, 93) = 18.20$, $p < .001$, $\eta_p^2 = 0.37$, observed power =1.00). Participants reported meaningful reductions in symptoms using global impression of change scores when comparing baseline (*M* = 4.03, *SD* = 0.03) to months one (*M* = 3.50, *SD* = 0.16), two (*M* = 3.03, *SD* = .15), and three (*M* = 3.03, *SD* = 0.18) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time ($F(3, 93) = 0.38$, $p = 0.77$, $\eta_p^2 = 0.01$, observed power = 0.12) or main effect of dosing condition ($F(1, 31) = .01$, $p = .69$, $\eta_p^2 = 0.01$, observed power = 0.07) on global impression of change scores.

A 2x4 mixed ANOVA revealed a meaningful main effect of time on subjective severity ratings of MRS (Greenhouse-Geisser Adjusted; $F(2.21, 68.51) = 7.50$, $p < .001$, $\eta_p^2 = 0.20$, observed power = 0.95). Participants yielded meaningfully higher baseline subjective severity ratings of MRS ($M = 2.69$, $SD = 0.10$) compared to months one ($M = 2.24$, $SD = 0.12$), two ($M = 2.15$, $SD = 0.08$), and three ($M = 2.09$, $SD = 0.13$) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time (Greenhouse-Geisser Adjusted; $F(2.21, 68.51) = 0.24$, $p = 0.81$, $\eta_p^2 = 0.01$, observed power = 0.09) or main effect of dosing condition ($F(1, 31) = 0.94$, $p = 0.34$, $\eta_p^2 = 0.03$, observed power = 0.16) on subjective severity ratings of MRS.

Anxiety

A 2x4 mixed ANOVA revealed a meaningful main effect of time on anxiety scores ($F(3, 93) = 3.67$, $p < .015$, $\eta_p^2 = 0.11$, observed power = 0.79). Participants reported meaningfully higher baseline anxiety ($M = 8.60$, $SD = 1.19$) compared to months one ($M = 5.37$, $SD = .92$), two ($M = 6.55$, $SD = .96$), and three ($M = 5.96$, $SD = 1.13$) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time ($F(3, 93) = 0.36$, $p = 0.78$, $\eta_p^2 = 0.01$, observed power = 0.12) or main effect of dosing condition ($F(1, 31) = 0.94$, $p = 0.34$, $\eta_p^2 = 0.03$, observed power = 0.16) on anxiety scores.

Stress

A 2x4 mixed ANOVA revealed a meaningful main effect of time on stress scores (Greenhouse-Geisser Adjusted; $F(2.44, 75.67) = 4.20$, $p = 0.02$, $\eta_p^2 = 0.12$, observed power = 0.78). Participants yielded meaningfully higher baseline stress ($M = 12.67$, $SD = 1.37$) compared to months one ($M = 10.14$, $SD = 1.20$), two ($M = 9.86$, $SD = 1.16$), and

three (*M* = 8.61, *SD* = 1.12) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time (Greenhouse-Geisser Adjusted; $F(2.43, 75.39) = 0.25$, $p = 0.82$, $\eta_p^2 = 0.01$, observed power = 0.10) or main effect of dosing condition ($F(1, 31) = 0.01$, $p = 0.93$, $\eta_p^2 = 0.00$, observed power = 0.05) on stress scores.

Irritability

A 2x4 mixed ANOVA revealed a meaningful main effect of time on irritability scores (Greenhouse-Geisser Adjusted; $F(2.01, 62.15) = 3.22$, $p = .047$, $\eta_p^2 = .10$, observed power = .60). Participants yielded meaningfully higher baseline irritability (*M* = 13.52, *SD* = .71) compared to months one (*M* = 11.76, *SD* = .58), two (*M* = 11.80, *SD* = .60), and three (*M* = 11.59, *SD* = .62) of CBD administration. Findings revealed no meaningful interaction effect between dosing condition and time (Greenhouse-Geisser Adjusted; $F(2.01, 62.15) = 0.61$, $p = 0.61$, $\eta_p^2 = 0.02$, observed power = 0.17) or main effect of dosing condition ($F(1, 31) = 2.07$, $p = 0.16$, $\eta_p^2 = 0.06$, observed power = 0.29) on irritability scores.

Sleep

A 2x4 mixed ANOVA revealed no meaningful interaction effects between dosing condition and time on global sleep quality scores ($F(3, 93) = 0.87$, $p = 0.46$, $\eta_p^2 = 0.03$, observed power = 0.23) and no meaningful main effects of dosing condition ($F(1, 31) = 1.34$, $p = 0.27$, $\eta_p^2 = 0.04$, *observed power* = .20) or time ($F(3, 93) = 0.98$, $p = 0.41$, $\eta_p^2 = 0.03$, observed power = 0.26).

Alcohol Use

A 2x4 mixed ANOVA revealed no meaningful interaction effects between dosing condition and time on alcohol use (Greenhouse-Geisser Adjusted; $F(2.28, 70.70) = 0.34$, $p = 0.74$, $\eta_p^2 = 0.01$, observed power = 0.11) and no meaningful main effects of dosing condition ($F(1, 31) = 2.76$, $p = 0.11$, $\eta_p^2 = 0.08$, observed power = 0.36) or time (Greenhouse-Geisser Adjusted; $F(2.28, 70.70) = 1.16$, $p = 0.33$, $\eta_p^2 = 0.04$, observed power = 0.26).

Depression

A 2x4 mixed ANOVA revealed no meaningful interaction effects between dosing condition and time on depression scores ($F(3, 93) = 0.13$, $p = 0.94$, $\eta_p^2 = 0.00$, observed power = 0.07) and no meaningful main effects of dosing condition ($F(1, 31) = 0.38$, $p = 0.54$, $\eta_p^2 = 0.01$, observed power = 0.09) or time ($F(3, 93) = 2.27$, $p = 0.09$, $\eta_p^2 = 0.07$, observed power = 0.56).

VAMS-Mood

A 2x4 mixed ANOVA revealed no meaningful interaction effects between dosing condition and time on mood scores ($F(3, 93) = 2.41$, $p = 0.07$, $\eta_p^2 = 0.07$, observed power = 0.59) and no meaningful main effects of dosing condition ($F(1, 31) = 0.13$, $p = 0.72$, $\eta_p^2 = 0.00$, *observed power* = 0.06) or time ($F(3, 93) = 0.02$, $p = 0.99$, $\eta_p^2 = 0.00$, observed power = 0.05).

Discussion

Given that CBD has been demonstrated to yield a range of possible therapeutic effects on symptoms that overlap with MRS (i.e., anxiety, sleep disturbance, migraine) and the relative lack of side-effects associated with CBD, it is reasonable to consider that

CBD may be a viable option for MRS intervention. The current study aimed to examine the potential effects of orally ingested CBD isolate for alleviating both physical and psychological MRS. Results revealed meaningful reductions in monthly ratings of MRS (using the MRSQ), subjective severity of symptoms, global impression of change, anxiety, irritability, and stress in both conditions when comparing baseline to months one, two, and three of CBD administration. There were no meaningful reductions (or other impacts) on monthly ratings of depression, sleep quality, and alcohol use when comparing baseline to all three months of CBD administration. Taken together, findings suggest that CBD may have potential for treating MRS and related health outcomes; further investigation is warranted.

Though past research has suggested cannabis may be a viable option for MRS intervention (Baron, 2018; Carlini & Cunha, 1981; Shannon et al., 2019), to our knowledge this study is the first to test the effects of CBD on MRS. Current study findings are consistent with past research showing the therapeutic effects of CBD on various experiences associated with MRS. For example, results showed reductions in monthly ratings of MRS (using the MRSQ, subjective severity, global impression of change), pain, stress, and anxiety (i.e., Zuardi et al., 2017). Inconsistent with past research, we found no impact on sleep quality when comparing baseline to all months of CBD administration. We offer several potential explanations for the current study outcomes in the context of the extant literature.

MRS was measured using a variety of outcomes, including the MRSQ (which accounts for physiological and psychological symptoms), subjective severity of MRS experiences, and global impression of change, which all showed reductions in symptoms

among both dosing conditions for all months of CBD administration compared to baseline. Further, we examined distinctive types of symptoms of the MRSQ (physiological, psychological, appetite), showing reductions in both physiological and psychological symptoms, which is consistent with past literature documenting effects of CBD on both experiences (i.e., pain, anxiety; Bergamaschi et al., 2011; Boyaji et al., 2020; Resstel et al., 2009), as well as appetite-related symptoms. Past research has documented the therapeutic effects of CBD on pain, and consistent with past research, findings showed reductions in physiological symptoms, such as headaches; however, various physiological symptoms that are assessed in the MRSQ have not been examined in relation to CBD (i.e., abdominal bloating, nausea; Boyaji et al., 2020; Sexton et al., 2016) and future research is warranted. Though most research suggesting that cannabis reduces the experience of pain is in reference to THC, CBD has been associated with reducing pain that is a result of inflammation (i.e., Boyaji et al., 2020; Burstein, 2015; Johnson et al., 2010). To the extent that some physiological MRS may be a result of inflammation, CBD may reduce some physiological symptoms.

In the literature, the effect of CBD on anxiety symptoms is found to be effective at higher doses (300-600mg), but not lower doses (Bergamaschi et al., 2011; Zuardi et al., 2017); the current study's findings are consistent with past literature as we observed reductions in the 320mg condition, however, we also found reductions in the 160mg condition (though trends suggest a small dose effect that is consistent with past literature; see Figure 3). Data also revealed reductions in stress symptoms in both conditions (showing no dose effect) between baseline and all months of CBD administration. Further, this study is the first of our knowledge examining the effect of CBD on

irritability symptoms; findings showed a small reduction in irritability symptoms among both conditions, in all three cycles of CBD administration when compared to baseline. Though recent work has suggested that medicinal cannabis may be effective in reducing depressive symptoms among clinically relevant populations (Martin et al., 2021), current study findings indicated no impact on depression symptoms (which were generally low in the current study sample) when comparing all three months of CBD administration to baseline.

Though CBD has been implicated throughout the literature to increase sleep quality, we found no impact on sleep quality, however, current study participants reported good sleep quality at baseline and throughout the study. Recent work has shown that CBD may function as a neuroprotective factor and treatment for alcohol use (e.g., De Ternay et al., 2019; Nona et al., 2019; Turna et al., 2019). Further, greater alcohol use is associated with more severe experiences of MRS (Carroll et al., 2015; Epstein et al., 2006; Strine et al., 2005). Findings indicated no impact on alcohol use when comparing all months of CBD administration to baseline; however, we used a homogeneous low-consuming sample with respect to alcohol use and further research is warranted investigating the impact of CBD on alcohol use.

There are several strengths of the current study that should be noted. First, participants consumed CBD for 5 days during each cycle for three consecutive months. Because of acute dosing (the CBD from the previous month will have already been largely metabolized), each month can be viewed as a replication. Results showed similar reductions throughout all months and across all measures. Further, we employed well-validated measures to assess MRS and related constructs. Additionally, we used a novel

dosing paradigm that was a hybrid of acute and chronic dosing. Future work could examine differences in acute versus prolonged dosing of CBD for the treatment of MRS as different dosing strategies yields different outcomes. Though the current study's findings provide early evidence for the utility of CBD as a treatment for MRS and there were several strengths, various limitations should be noted. First, we used a relatively homogenous sample that potentially oversampled individuals who suffer from similar severity of MRS. Though having a homogenous sample with regards to MRS promotes reductions of potential confounds, it is possible that CBD may only affect a certain range of symptom severity; individuals diagnosed with PMDD or who have more severe MRS may not see the same effect. Future work could examine a range of symptom severity or clinically relevant samples of individuals who suffer from severe MRS or PMDD to further assess the utility of CBD as a potential treatment strategy for treating more severe MRS. Second, the current study relied on individuals self-reporting that they ingested CBD at prescribed times and doses; we did this to reduce attrition as participants were enrolled in this study for four consecutive months. Future studies could verify participant behavior.

Third, the current study did not implement a placebo control. It is possible that the reductions we see from baseline to all six months of intervention may result from a placebo effect, as various expectancy effects have been documented on a range of symptoms that are associated with MRS, such as pain, anxiety, and stress, (e.g., Altman et al., 2021; De Vita et al., 2021; Spinella et al., 2021). Future work could investigate the therapeutic efficacy of CBD for MRS using a placebo-controlled trial. Therefore, further research is warranted examining the utility of CBD in treating MRS as well as the

potential to optimize CBD administration for reducing MRS (i.e., terpenes, routes of administration, time of administration). Future work should also investigate the efficacy of CBD used acutely on days when individuals experience symptoms versus chronically with respect to MRS.

Further, given that symptom expression of MRS is variable between and among individuals who experience it, many individuals did not meet criteria for study inclusion because their cycles did not meet the requirement for a experiencing a regular period (occurring every 21-38 days). Missing cycles and irregular periods are very common as many individuals experience stressors or situations that impact the timing of their menstrual cycle (hormonal imbalance, socioeconomic status, pandemic-related stress; Kwak et al., 2019; Ozimek et al., 2021). Future research could account for this variability by using samples that consist of both regular and irregular periods. Last, we did not validate which cycle phase participants were experiencing at any point of the study, and further research could investigate the utility of CBD for MRS across different phases of the menstrual cycle using salivary progesterone concentrations.

Despite limitations, the current study suggests that CBD may be an effective treatment in alleviating MRS, both physiologically and psychologically. Given the prevalence of MRS, as well as the relative lack of effective treatments in treating the entirety of experiences that occur because of MRS, an alternative treatment strategy is warranted. Taken together, with the findings of the current study, it is reasonable to consider and further investigate CBD as a viable option for MRS intervention. This study provides early evidence for CBD as a treatment alternative for MRS and more research is needed to further determine the utility and to optimize CBD administration for reducing

MRS with various possibilities for future directions (i.e., with the use of terpenes, using individuals with more severe MRS, investigating the simultaneous effects of birth control and CBD).

Tables

Table 1.
Descriptive Statistics of Screener Data

	N	M	SD	Min	Max
Age	481	20.52	2.80	18.00	42.00
BMI	576	23.11	3.67	13.35	42.98
Age at Menarche	577	12.53	1.49	7.00	17.00
MRSQ	577	53.59	11.50	26.00	96.00
DASS—Depression	577	8.98	9.27	00.00	42.00
DASS—Anxiety	577	7.12	7.25	00.00	38.00
DASS—Stress	577	11.40	8.34	00.00	42.00
BITE—Total	577	14.44	4.23	5.00	29.00
PSQI Global	577	7.16	3.14	1.00	20.00
DAST Total	577	1.21	1.07	0.00	16.00
AUDIT Total	577	3.89	3.69	0.00	30.00
BITe Total	577	14.44	4.23	5.00	29.00
Subjective Severity Rating	577	2.49	.65	1.00	4.00

Note. 84% Caucasian, 6% Asian American, 3% African American, 2% Middle Eastern, 5% other; 93% not Hispanic or Latino/x.

Table 2.

Screener Bivariate Correlations Between MRSQ and Related Constructs

Variable	1	2	3	4	5	6	7	8	9
1. MRSQ	-	.42	.47	.55	.55	.36	.65	.02	.10
2. Depression		-	.55	.63	.42	.46	.33	.00	.14
3. Anxiety			-	.72	.36	.35	.35	.06	.09
4. Stress				-	.54	.45	.38	.01	.13
5. Irritability					-	.30	.39	.03	.09
6. Sleep Quality						-	.22	-.01	.10
7. Subjective Severity							-	.07	.02
8. Drug Abuse								-	.21
9. Alcohol Use									-

Note. $N = 577$.

Table 3.
Participant Screener Descriptive Statistics

	M	SD	Min	Max
Age	20.50	2.63	18.00	28.00
BMI	23.09	2.68	19.05	29.68
Age at Menarche	12.48	1.20	10.00	14.00
MRSQ	54.85	12.02	34.00	87.00
DASS—Depression	8.06	6.92	00.00	24.00
DASS—Anxiety	8.00	9.18	00.00	38.00
DASS—Stress	12.67	7.38	2.00	30.00
BITE—Total	14.24	4.23	6.00	27.00
PSQI Global	7.40	3.82	2.00	17.00
DAST Total	1.03	0.92	0.00	4.00
AUDIT Total	3.45	3.27	0.00	11.00
Subjective Severity Rating	2.52	0.51	2.00	3.00

Note. N = 33. 79% Caucasian, 12% Bi-racial; 3% Asian American, 3% Middle Eastern, 3% other; 93.94% Non-Hispanic or Latino/x.

Table 4.
Descriptive Statistics of MRS Monthly Health Outcomes

	Month	***M***	***SD***	***Min***	***Max***
MRSQ	Baseline	51.55	10.13	38.00	85.00
	1	45.00	8.37	31.00	72.00
	2	41.03	5.89	31.00	56.00
	3	41.88	7.01	30.00	59.00
MRSQ-Physiological	Baseline	25.82	5.90	16.00	46.00
	1	22.88	3.79	16.00	33.00
	2	21.24	3.78	16.00	32.00
	3	21.55	21.55	16.00	29.00
MRSQ-Psychological	Baseline	20.97	4.81	12.00	31.00
	1	18.42	5.65	11.00	33.00
	2	16.09	2.82	11.00	22.00
	3	16.67	4.11	11.00	28.00
MRSQ-Appetite	Baseline	4.76	1.71	2.00	8.00
	1	3.70	1.29	2.00	6.00
	2	3.70	1.26	2.00	7.00
	3	3.67	1.27	2.00	6.00
Subjective Severity	Baseline	2.70	0.59	2.00	4.00
	1	2.24	0.66	1.00	4.00
	2	2.15	0.44	1.00	4.00
	3	2.09	0.72	1.00	4.00
Period Progress	Baseline	4.03	0.17	4.00	5.00
	1	3.48	0.91	2.00	5.00
	2	3.03	0.85	1.00	5.00
	3	3.03	1.02	1.00	5.00

Note. $N = 33$.

Table 5.
Descriptive Statistics of Other Monthly Health Outcomes

	Month	***M***	***SD***	***Min***	***Max***
DASS-Anxiety	Baseline	8.61	6.72	0.00	24.00
	1	5.40	5.23	0.00	20.00
	2	6.49	5.55	0.00	20.00
	3	6.00	6.52	0.00	28.00
DASS-Depression	Baseline	8.85	6.65	0.00	20.00
	1	6.06	5.37	0.00	20.00
	2	6.61	6.60	0.00	24.00
	3	7.94	7.94	0.00	32.00
DASS-Stress	Baseline	12.67	7.74	0.00	28.00
	1	10.12	6.78	0.00	30.00
	2	9.88	6.58	0.00	24.00
	3	8.61	6.31	0.00	24.00
BITe	Baseline	13.48	4.14	7.00	23.00
	1	11.73	3.44	6.00	20.00
	2	11.79	3.39	5.00	19.00
	3	11.58	3.49	5.00	19.00
PSQI	Baseline	5.94	3.61	1.00	17.00
	1	5.36	3.19	1.00	14.00
	2	5.97	2.82	2.00	13.00
	3	5.70	2.94	2.00	13.00
AUDIT	Baseline	4.15	3.47	0.00	10.00
	1	3.70	3.02	0.00	9.00
	2	3.97	3.67	0.00	13.00
	3	3.73	3.24	0.00	12.00
VAMS	Baseline	26.27	18.27	0.00	83.00
	1	26.61	16.71	0.00	78.00
	2	26.88	20.53	0.00	87.00
	3	27.03	18.58	0.00	82.00

Note. $N = 33$.

Figures

Figure 1.

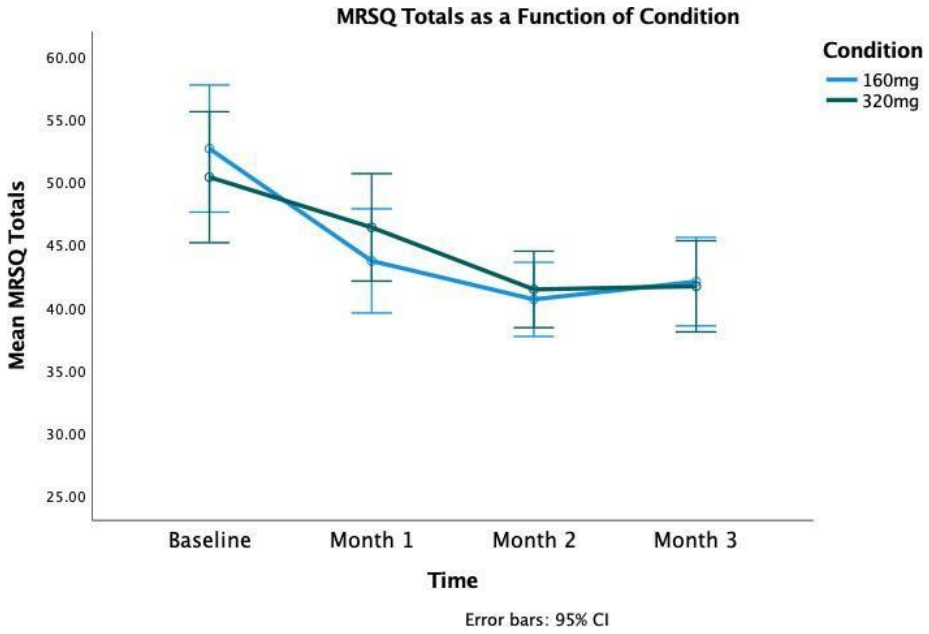


Figure 2.

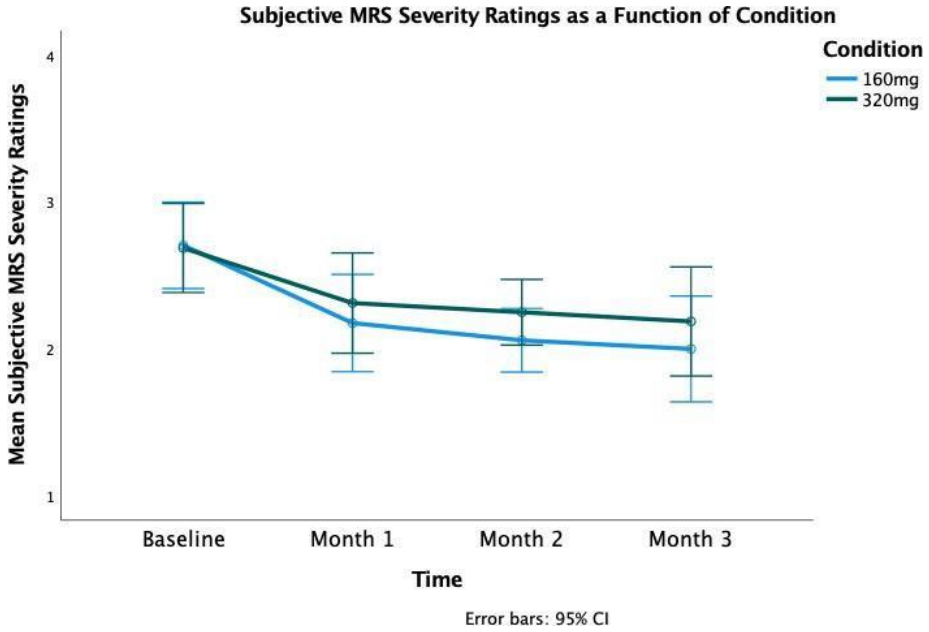

Subjective MRS Severity Ratings as a Function of Condition
Condition
160mg
320mg
Mean Subjective MRS Severity Ratings
4
3
2
1
Baseline
Month 1
Month 2
Month 3
Time
Error bars: 95% CI

Figure 3.

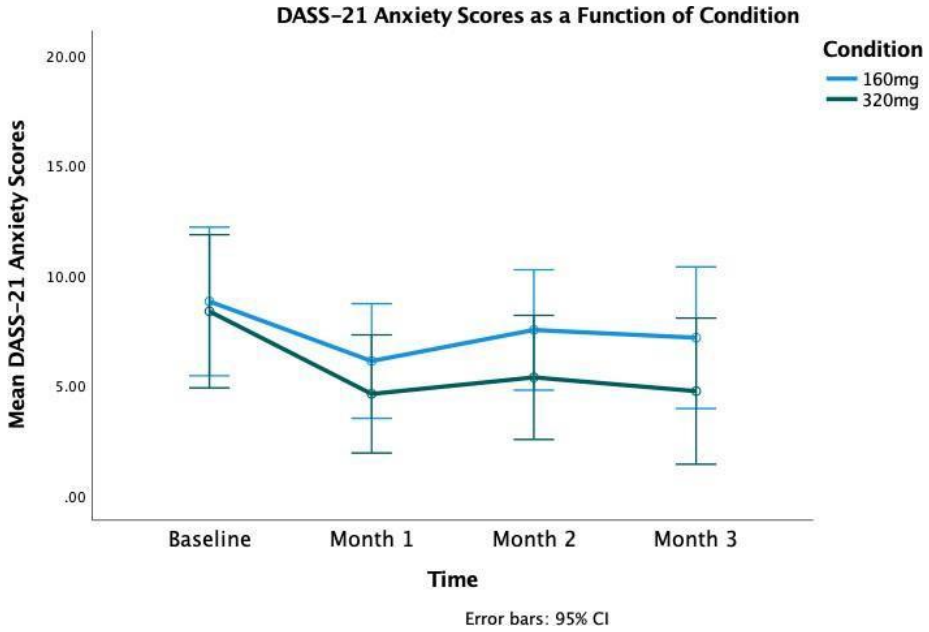

DASS-21 Anxiety Scores as a Function of Condition
Condition
160mg
320mg
Mean DASS-21 Anxiety Scores
20.00
15.00
10.00
5.00
.00
Baseline
Month 1
Month 2
Month 3
Time
Error bars: 95% CI

Figure 4.

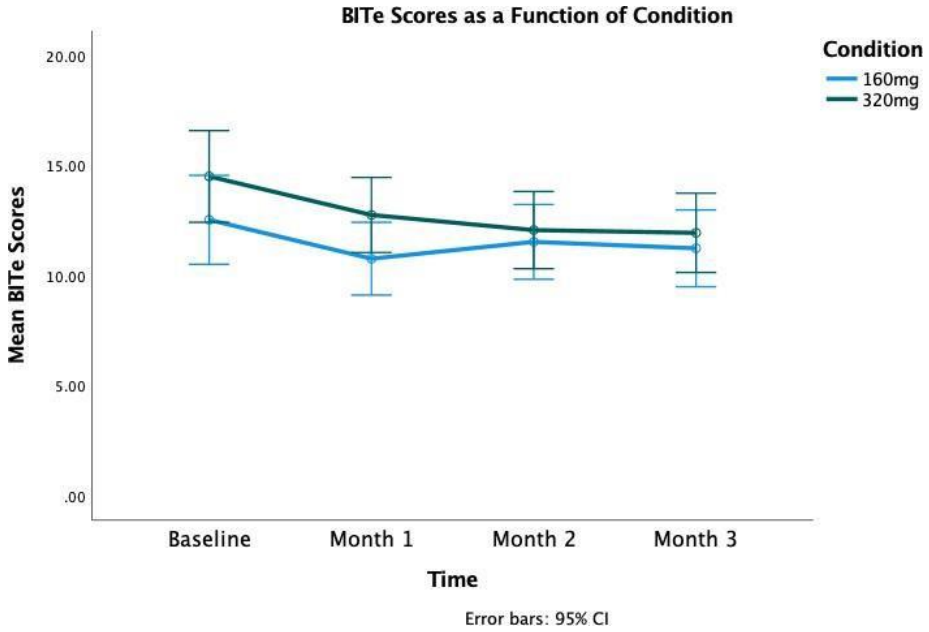

BITe Scores as a Function of Condition
Condition
160mg
320mg
Mean BITe Scores
20.00
15.00
10.00
5.00
.00
Baseline
Month 1
Month 2
Month 3
Time
Error bars: 95% CI

Figure 5.

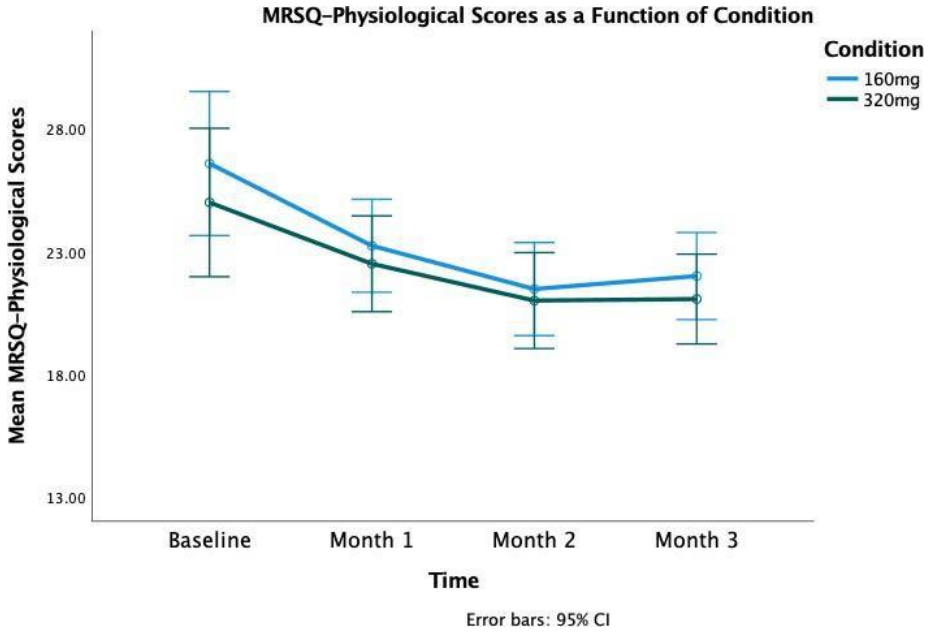

MRSQ–Physiological Scores as a Function of Condition
Condition
160mg
320mg
Mean MRSQ–Physiological Scores
28.00
23.00
18.00
13.00
Baseline
Month 1
Month 2
Month 3
Time
Error bars: 95% CI

Figure 6.

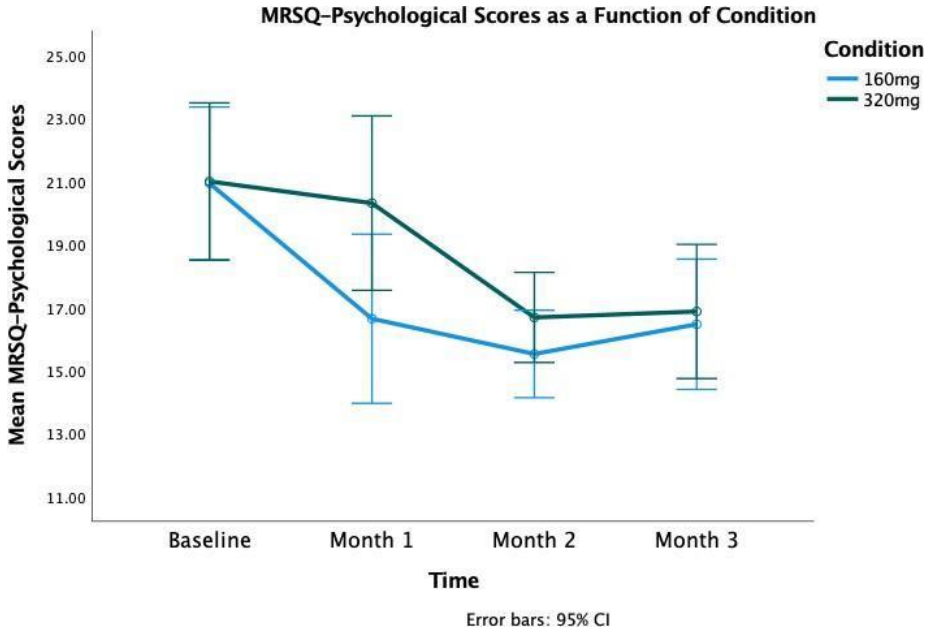
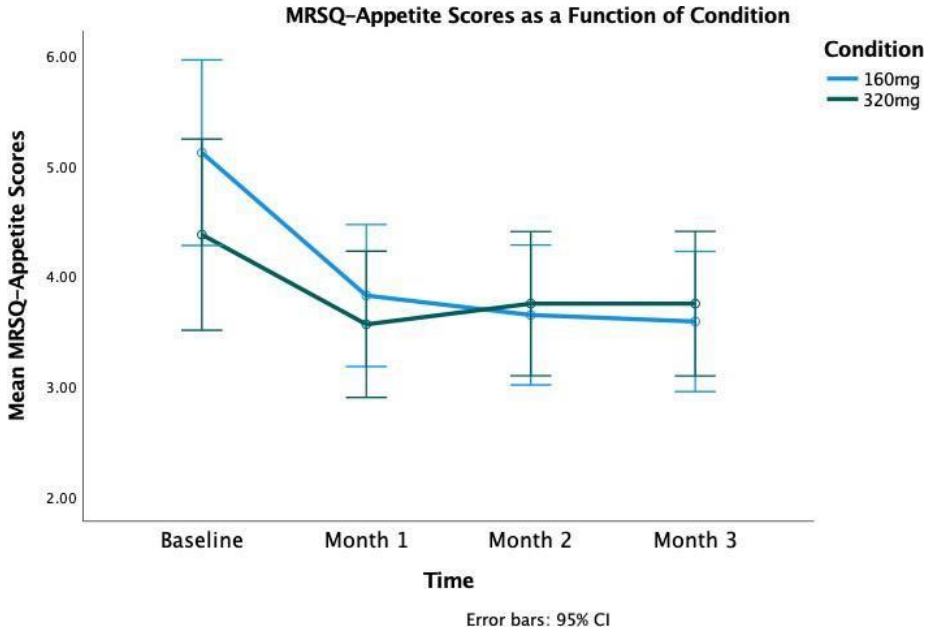

MRSQ–Psychological Scores as a Function of Condition
Condition
160mg
320mg
Mean MRSQ–Psychological Scores
25.00
23.00
21.00
19.00
17.00
15.00
13.00
11.00
Baseline
Month 1
Month 2
Month 3
Time
Error bars: 95% CI

Figure 7.


MRSQ–Appetite Scores as a Function of Condition
Condition
160mg
320mg
Mean MRSQ–Appetite Scores
6.00
5.00
4.00
3.00
2.00
Baseline
Month 1
Month 2
Month 3
Time
Error bars: 95% CI

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