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Examination of the Effects of Cannabidiol on Menstrual-Related Symptoms

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Some individuals attempt to alleviate menstrual-related symptoms (MRS) by using cannabis and report having expectations that cannabis can improve MRS; however, no study has examined the effect of cannabinoids on MRS. The present study is a pre–post, randomized, open-label trial that aimed to examine the effects of oral cannabidiol (CBD) isolate for alleviating MRS. Participants were assigned randomly to one of two open-label dosing groups of CBD softgels (160 mg twice a day, BID, $n = 17$; 320 mg BID, $n = 16$) and completed a 1-month baseline period. Following baseline, participants were instructed to consume CBD starting the first day they believed they experienced symptoms each month and to take their assigned dose daily for 5 consecutive days for three CBD-consumption months. We examined differences in MRS and related outcomes between baseline and 3 months of CBD consumption. Results revealed reductions (in both dosing groups) in MRS, irritability, anxiety, global impression of change, stress, and subjective severity scores when comparing baseline to all 3 months of CBD consumption. Depression scores did not change in either dosing group. Findings suggest that CBD may have the potential for managing MRS. Importantly, changes in symptoms appeared in the first month of CBD consumption and persisted over the 3 consumption months. Further research is warranted comparing the effects of CBD to placebo (a limitation of the study) and examining the potential to optimize CBD consumption for reducing MRS (e.g., combining CBD with terpenes; varying routes and timing of administration).

Public Health Significance

The present study serves as the first to investigate the potential therapeutic impacts of CBD for menstrual-related symptoms. Findings suggest CBD may be effective in alleviating menstrual-related symptoms, and placebo-controlled studies are needed.

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

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Materials and analysis code for this study are available by emailing the corresponding author. This study was registered with https://Clinicaltrials.gov (Identifier NCT05679830) and was not completed under an Investigational New Drug. This study has been presented at the 32nd Annual International Cannabinoid Research Society Symposium on the Cannabinoids in 2022.

Morgan L. Ferretti and Jessica G. Irons had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of its presentation.

Morgan L. Ferretti played a lead role in project administration and writing–original draft and an equal role in conceptualization. Taylor B. Stanley played an equal role in conceptualization, methodology, and writing–review and editing. Erica N. Peters played a supporting role in conceptualization and writing–review and editing. Marcel O. Bonn-Miller played a supporting role in conceptualization and an equal role in writing–review and editing. Jessica G. Irons played a lead role in supervision and writing–review and editing, a supporting role in writing–original draft, and an equal role in conceptualization.

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Approximately 75% of menstruating individuals experience unpleasant menstrual-related symptoms (MRS; Wakil et al., 2012). MRS include both physiological (e.g., cramps, headache, breast tenderness) and psychological (e.g., irritability, tension, depressed mood) symptoms (Yonkers et al., 2008). Studies suggest that 5%–8% of menstruating individuals 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., 2007).

MRS expression varies between a few days and 2 weeks and often worsens approximately 6 days before and peaks at 2 days prior to menstruation (Meaden et al., 2005; Pearlstein et al., 2005). MRS can occur in all phases of the menstrual cycle (i.e., menstrual, follicular, ovulatory, luteal; Handy et al., 2022; Reed et al., 2008); therefore, all symptoms that are attributable to the menstrual cycle can be considered MRS. Though MRS have been extensively studied, more clinical research is necessary because of its impact on everyday life, relationships, and economic losses (Halbreich et al., 2003), as well as because of the association between MRS and psychiatric symptomatology and diagnosis (Gonda et al., 2008). Specifically, menstruation is associated with exacerbations of mood and anxiety disorders such as major depression (Kornstein et al., 2005), panic disorder (Breier et al., 1986; B. L. Cook et al., 1990; Kaspi et al., 1994), bipolar disorder (Rasgon et al., 2003), and others (Allen, 1996; S. M. Evans et al., 2002; Lester et al., 2003).

Though MRS are prevalent and often debilitating, effective remedies for managing symptoms are scarce. Individuals with mild symptoms might manage symptoms through lifestyle changes (e.g., diet modification; Dickerson et al., 2003), use of over-the-counter (OTC) pain medications (e.g., ibuprofen), or behavioral remedies (e.g., heating pad); however, these strategies are often ineffective for individuals who experience more severe symptoms (Dickerson et al., 2003; Marjoribanks et al., 2015). Most available intervention strategies for MRS have focused largely on physiological symptoms, and little clinical research (and few potential intervention strategies) aims to study and improve psychological MRS. Clinically relevant psychological symptoms are most often treated with pharmacotherapy (e.g., selective serotonin reuptake inhibitor's) or hormonal interventions (e.g., birth control); however, these interventions have only shown clinically relevant improvement in approximately 60% of those who engage with the interventions (Pearlstein & Steiner, 2012), and side effects often occur with use (i.e., nausea, night sweats; Dimmock et al., 2000).

Given the prevalence and salience of MRS and the relative paucity of remedies, consideration of novel intervention strategies is warranted. One intervention strategy with the potential to impact a wide range of symptoms that overlap with MRS is cannabidiol (CBD; Russo et al., 2007; Russo & Hohmann, 2013; Slavin et al., 2017). CBD (whole plant, isolate, and targeted formulations) has been demonstrated to yield a range of possible therapeutic effects (e.g., mood regulation, neuroprotection, analgesic effects, anti-inflammation, reduced anxiety, and immunomodulatory effects; e.g., Andreae et al., 2015; Lopez et al., 2020; Schier et al., 2012; Shannon et al., 2019; Zuardi et al., 1993, 2006); further, therapeutic effects of CBD for pain and physiological MRS have both been associated with inflammation (Barcikowska et al., 2020; Burstein, 2015; Gold et al., 2016). Another benefit of CBD as a form of intervention is its relative safety compared to other currently available treatments for MRS (e.g., OTC pain medications, selective serotonin reuptake inhibitors), which have been associated with various adverse side effects (Cascade et al., 2009; W. B. Cook & Dallas, 2008; Ferguson, 2001), abuse (E. A. Evans & Sullivan, 2014; Wolf et al., 2012), and/or overdose (Elflein, 2023; Wolf et al., 2012). For example, OTC medications are associated with nausea and drowsiness (W. B. Cook & Dallas, 2008). Similarly, selective serotonin reuptake inhibitors are associated with dizziness, nausea, weight gain, and agitation (Cascade et al., 2009; Ferguson, 2001). According to exhaustive reviews, both healthy individuals and clinical populations do not typically experience adverse effects from acute or chronic exposure to CBD (Iffland & Grotenhermen, 2017; Larsen & Shahinas, 2020).

Recent literature suggests that some individuals attempt to alleviate MRS by using cannabis and report having expectations that cannabis can improve MRS (Hanzal et al., 2019; Joyce et al., 2021; Slavin et al., 2017). Slavin et al. (2017) found that individuals reported expectancies that cannabis would alleviate all symptoms associated with MRS except for overeating/food cravings. Given the considerable overlap in symptoms impacted positively by CBD and MRS (e.g., anxiety, depressive symptoms, sleep problems) and the relative lack of side effects associated with CBD, CBD may be a viable option for MRS improvement. Although research has suggested cannabinoids as a potential alternative treatment for MRS (Hanzal et al., 2019; Joyce et al., 2021; Slavin et al., 2017), no study to date has directly evaluated the effect of CBD on MRS. The present study aims to examine the effects of orally ingested CBD isolate softgels on MRS and related psychological outcomes (i.e., depression, anxiety, stress, irritability).

Method

Participants

Participants ($N = 33$; $M_{age} = 20.50$, $SD_{age} = 2.63$; $M_{BMI} = 23.02$, $SD_{BMI} = 2.68$) were individuals who self-reported experiencing normal menstruation (occurring every 21–38 days and lasting between 4 and 8 days; Creinin et al., 2004), willingness to track their menstrual cycles systematically, and experiencing MRS (see Table 1, for all sample demographics). Individuals were excluded from participation by reporting being under the age of 18 or greater than 55, using cannabis or cannabis-containing products within 30 days of screening, current effort to become pregnant, a history of suicide attempt, or endorsed plans for suicide within the last year, a BMI of underweight (<18 kg/m^2) or obese (>30 kg/m^2), or having a *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* diagnosis (e.g., current psychotic disorder) or significant disease or disorder (e.g., epilepsy). See Table 2 for all eligibility criteria. One individual withdrew from the study because of an adverse event (skin irritation) after consuming one CBD dose. Participants were recruited via university bulk email, inviting those who experience MRS to complete an electronic screener via QuestionPro that included the Menstrual-Related Symptom Questionnaire (MRSQ) and all eligibility criteria (Table 1). Individuals who met criteria ($N = 537$) were then contacted via email, and those who were interested in enrolling attended a screening session (via Zoom) that included informed consent and eligibility procedures; all participants who completed a virtual screening session were rescreened for all eligibility criteria, met all criteria, and completed informed consent ($N = 68$). See Figure 1 for participant flow.

Table 1
Participant Screener Descriptive Statistics

	160 mg (n = 17)		320 mg (n = 16)		
Demographic	*M*	*SD*	*M*	*SD*	*T* statistic (*p* value)
Age	20.88	2.67	20.07	2.60	0.87 (.39)
BMI	22.65	3.14	23.411	2.12	0.81 (.21)
Age at menarche	12.71	1.26	12.25	1.13	1.09 (.28)
MRSQ total	56.88	13.06	52.68	10.80	1.00 (.32)
DASS-depression	8.47	7.99	7.63	5.81	0.35 (.73)
DASS-anxiety	9.18	9.17	6.75	9.32	0.75 (.46)
DASS-stress	12.71	6.82	12.63	8.16	0.03 (.98)
BITe-total	13.82	5.08	14.688	3.38	0.57 (.57)
Subjective severity	2.53	0.51	2.50	0.52	0.16 (.87)

Note. N = 33. 79% Caucasian, 12% biracial; 3% Asian American, 3% Middle Eastern, 3% other; 93.94% non-Hispanic or Latino/x. BMI = body mass index; MRSQ = Menstrual-Related Symptoms Questionnaire; DASS = Depression Anxiety Stress Scale; BITe = Brief Irritability Test.

Materials

All internal consistency data are presented as ranges to reflect internal consistency for all time points across which we collected data.

Demographics and Eligibility

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

MRSQ

The MRSQ is a 26-item measure adapted (and validated) from the Menstrual-Symptom Questionnaire (Chesney & Tasto, 1975) that includes assessment of common physiological and psychological symptoms that individuals may experience because of menstruation (Ferretti et al., 2022). Respondents report the severity of each symptom on a 4-point Likert scale (1 = *none* to 4 = *severe*). Scores from individual items are summed to create a total score that ranges from 26 to 104 with higher scores indicating more severe experiences of MRS. The MRSQ shows construct and criterion validity evidence among a sample of menstruating, college-aged individuals (Ferretti et al., 2022). Internal consistency for this sample is good (Cronbach's α range = .77–.89).

Brief Irritability Test

The Brief Irritability Test (BITe) is a five-item self-report measure used to evaluate irritability symptoms over the past 2 weeks (Holtzman et al., 2015). Each item appears on a 6-point Likert scale (1 = *never* to 6 = *always*). Items are summed to a create a total score with that ranges from 5 to 30, with higher scores indicating greater irritability. Internal consistency for this sample is good (Cronbach's α range = .83–.90).

Depression, Anxiety, and Stress Scale–21

The Depression, Anxiety, and Stress Scale–21 (DASS-21) is a 21-item self-report instrument used to assess symptoms of depression, anxiety, and tension/stress in the past week. Item responses are measured on a 4-point Likert scale (0 = *did not apply to me at all* to 3 = *applied to me very much or most of the time*); seven items are summed for each subscale (i.e., depression, anxiety, stress) and 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).

Global Impression of Change

Global impression of change (GIC) is measured on a single-item 7-point Likert scale used to capture participants' beliefs about the efficacy of the CBD they received to take for MRS (1 = *very much improved* to 7 = *very much worse*).

Subjective Severity

Subjective severity is measured on a single-item 4-point Likert scale used to capture participants' beliefs about the severity of their MRS (1 = *minimal, no effect on normal activities* to 4 = *severe, intolerable, prevents normal activities*).

Compliance Assessment

Participants self-reported daily whether they consumed CBD as instructed (i.e., yes/no).

Study Product

Participants received softgels containing 20 mg of hemp-derived CBD isolate in medium-chain triglyceride oil. Study product was manufactured in the United States for Canopy Growth Corporation according to current Good Manufacturing Practice 21 Code of Federal Regulations Part 111. An accompanying third-party certificate of analysis (Micro Quality Labs, Inc.) documented that the product contained 20 mg CBD, was free of delta-9-tetrahydrocannabinol and other cannabinoids, and lacked contaminants.

Procedure

Following informed consent and eligibility procedures, participants were assigned randomly to one of two open-label study groups (participants were aware of the dose they were receiving): (a) 160 mg twice a day doses (morning and night), four softgels per dose, n = 17; and (b) 320 mg twice a day doses (morning and night),

Table 2
Participant Eligibility Criteria

Inclusion criteria
1. At least 18 years old
2. Willing and able to provide informed consent and participate in the study for 4 months
3. Experiences a regular period (occurring every 21–38 days and lasting between 4 and 8 days)
4. Diagnosed with premenstrual dysphoric disorder or scores at least "30" on the MRSQ
5. Willing to begin tracking their menstrual cycle for the duration of the study
6. Agrees to abide by all study restrictions and comply with all study procedures.
Exclusion criteria
1. Has a known history of significant allergic condition, significant hypersensitivity to CBD, or allergic reaction to cannabis, cannabinoid medications, or excipients of the drug product
2. Has been exposed to any investigational drug or device within 30 days of screening or plans to take another investigational drug at any time during the study
3. Has self-reported using cannabis, synthetic cannabinoid or cannabinoid analogue (e.g., dronabinol, nabilone), synthetic cannabinoid receptor agonist (e.g., spice, K2), or any CBD or THC-containing product within 30 days of screening or during the study
4. Has a current or past primary *DSM-5* diagnosis that the Investigator(s) determines would interfere in treatment or interfere in evaluation of the study treatment (e.g., current psychotic disorder)
5. Currently prescribed medications with known THC or CBD interactions (e.g., warfarin, clobazam, valproic acid, phenobarbital, mTOR inhibitors, oral tacrolimus)
6. Trying to get pregnant
7. Is pregnant[a]
8. Has a history of suicide attempt in the last year
9. Endorses current suicidal plan and intent during screening
10. Has any other significant disease or disorder which, in the opinion of the investigator, may either put the student at risk because of participation in the study, may influence the result of the study, or affect the student's ability to participate in the study
11. Has a BMI of underweight (18 kg/m^2 and below) or obese (30 kg/m^2 and above)

Note. MRSQ = Menstrual-Related Symptoms Questionnaire; CBD = cannabidiol; THC = tetrahydrocannabinol; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders, fifth edition*; BMI = body mass index; mTor = mechanistic Target of Rapamycin.
[a] Female participants were given the option for pregnancy testing. All participants were told to use adequate birth control throughout the study.

eight softgels per dose, $n = 16$. Participants completed an electronic survey that included the MRSQ, the BITe, the DASS-21, the GIC, and the subjective severity assessment for one baseline month (one 15-min survey completed the day after they finished menstruating). After completing baseline measures, participants received a 3-month supply of CBD isolate and completed monthly surveys related to MRS. During subsequent intervention months, participants received daily email reminders with when and how much CBD they should be taking. On the first day, participants believed they experienced symptoms each month, participants consumed their assigned dose daily for 5 consecutive days (given normal periods average between 2 and 7 days; Cleveland Clinic, 2022). Additionally, we encouraged participants to consume CBD with food high in fat to promote bioavailability (Mozaffari et al., 2021; Stott et al., 2013). In total, participants received 120 (160 mg) or 240 softgels (320 mg). The university institutional review board approved the present study (No. 21-1937; James Madison University), and data were collected between September 2020 and September 2021. An Investigational New Drug application was not submitted to the Food and Drug Administration as the present study sought to examine structure–function endpoints among a healthy, nondiseased, population using a dietary supplement. This study was registered with https://Clinicaltrials.gov (Identifier NCT05679830). See Table 3 for a schedule of study procedures.

Data Analysis Plan

Data were analyzed using SPSS (Version 28.0). Data analysis included data from individuals who completed the study protocol. We used descriptive statistics to capture all sample characteristics throughout the study (Tables 4 and 5). Compliance assessment included comparing days consuming CBD to days instructed to consume CBD (i.e., 5 consecutive days beginning the first day of reported MRS). A series of mixed 2 (dose) × 4 (month) analyses of variance (ANOVAs) were conducted to examine potential changes in all health-related outcomes (i.e., MRSQ total scores, BITe total scores, GIC item, DASS-21 subscales, subjective severity item) from baseline to Months 1, 2, and 3 of CBD consumption between dosing conditions (160 mg and 320 mg). No simple effect analyses were conducted given that there were no observed interaction effects. Assumptions of normality were assessed using a skewness value of 2 and a kurtosis value of 4 (Kim, 2013); assumptions of normality were met across all variables with the exception of baseline Global Impression of Change and Month 3 DASS-21 anxiety. Given that repeated measures ANOVAs are fairly robust to violations of normality and that all other months for these variables met this assumption, these variables were not log transformed. When sphericity assumptions were violated, we used Greenhouse–Guisser adjusted statistics.

Results

Compliance Assessment

Participant compliance of CBD consumption as instructed for this sample was good. For Month 1, participants reported taking CBD for 87.88% of days (across all 33 participants). For Month 2, participants reported taking CBD for 90.91% of days (across all 33 participants). For Month 3, participants reported taking CBD for 87.27% of days (across all 33 participants).

Outcome Analyses

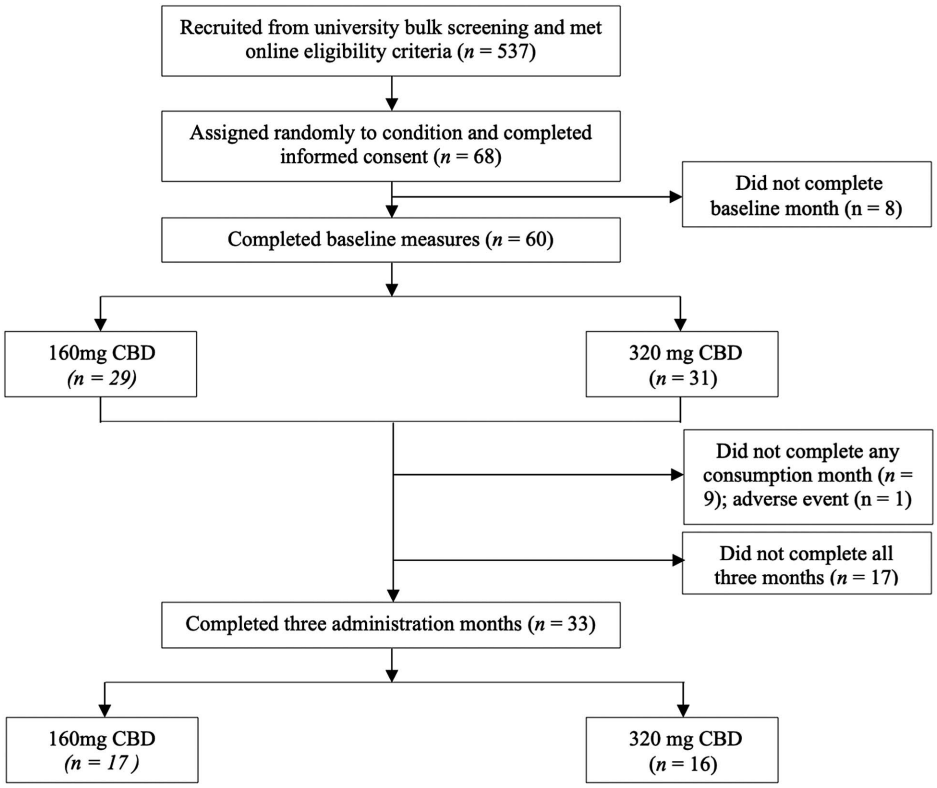
No interaction effects or main effects of the dosing condition occurred (see Table 6, for analyses of these effects).

MRS

A 2 × 4 mixed ANOVA revealed a 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.

Participants reported lower MRSQ scores during Months 1 ($M = 45.04$, $SD = 1.46$, $p < .001$), 2 ($M = 41.03$, $SD = 1.04$, $p < .001$), and 3 ($M = 41.87$, $SD = 1.24$, $p < .001$) of CBD consumption relative to baseline ($M = 51.51$, $SD = 1.78$; Figure 2).

Figure 1
CONSORT Flowchart of Participants



Note. Not all participants who were deemed eligible enrolled in the study. One participant in the 160 mg condition reported an adverse event (skin irritation) after taking CBD for one dose and was discontinued. All other participants who did not complete the study were due to attrition of not completing surveys during remote administration and are listed throughout the CONSORT. CONSORT = Consolidated Standards of Reporting Trials; CBD = cannabidiol.

A 2 × 4 mixed ANOVA revealed a 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 reductions in symptoms using global impression of change scores during Months 1 ($M = 3.50$, $SD = 0.16$, $p = .001$), 2 ($M = 3.03$, $SD = 0.15$, $p < .001$), and 3 ($M = 3.03$, $SD = 0.18$, $p < .001$) of CBD consumption relative to baseline ($M = 4.03$, $SD = 0.03$).

A 2 × 4 mixed ANOVA revealed a 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 reported lower subjective severity ratings of MRS during Months 1 ($M = 2.24$, $SD = 0.12$, $p = .010$), 2 ($M = 2.15$, $SD = 0.08$, $p < .001$), and 3 ($M = 2.09$, $SD = 0.13$, $p = .002$) of CBD consumption relative to baseline ($M = 2.69$, $SD = 0.10$).

Table 3
Study Schedule

	Study procedures completed	
Study time point (in months)	~15-min survey on the day following the end of menstruation	CBD consumption for 5 days starting the first day participants experienced symptoms
Baseline month	X	
Month 1 of CBD consumption	X	X
Month 2 of CBD consumption	X	X
Month 3 of CBD consumption	X	X

Note. The 15-min survey included the MRSQ, DASS-21, global impression of change, subjective serverity, and the BITe. MRSQ = Menstrual-Related Symptoms Questionnaire; DASS-21 = Depression, Anxiety, and Stress Scale–21; BITe = Brief Irritability Test; CBD = cannabidiol.

Table 4
Descriptive Statistics of MRS Health Outcomes by Condition Across All Months

Outcome	Month	160 mg (n = 17)			320 mg (n = 16)		
		M	*SD*	(Min, Max)	*M*	*SD*	(Min, Max)
MRSQ total	Baseline	52.65	12.85	(38.00, 85.00)	50.38	6.30	(40.00, 63.00)
	Month 1	43.71	6.84	(33.00, 55.00)	46.38	9.78	(31.00, 72.00)
	Month 2	40.65	6.02	(31.00, 55.00)	41.44	5.91	(32.00, 56.00)
	Month 3	42.06	7.34	(30.00, 59.00)	41.69	6.87	(31.00, 54.00)
Subjective severity	Baseline	2.71	0.59	(2.00, 4.00)	2.69	0.60	(2.00, 4.00)
	Month 1	2.18	0.73	(1.00, 4.00)	2.31	0.60	(1.00, 3.00)
	Month 2	2.06	0.24	(2.00, 3.00)	2.25	0.58	(1.00, 3.00)
	Month 3	2.00	0.61	(1.00, 4.00)	2.19	0.83	(1.00, 4.00)
Global impression of change	Baseline	4.00	0.00	(4.00, 4.00)	4.06	0.25	(4.00, 5.00)
	Month 1	3.35	0.93	(2.00, 5.00)	3.63	0.89	(2.00, 5.00)
	Month 2	3.00	0.79	(1.00, 4.00)	3.06	0.93	(1.00, 5.00)
	Month 3	3.06	0.97	(1.00, 5.00)	3.00	1.10	(1.00, 5.00)

Note. MRSQ = Menstrual-Related Symptoms Questionnaire; Min = minimum; Max = maximum; MRS = menstrual-related symptoms.

Anxiety

A 2 × 4 mixed ANOVA revealed a main effect of time on DASS-21 anxiety scores, $F(3, 93) = 3.67$, $p = .015$, $\eta_p^2 = 0.11$, observed power = 0.79. Participants reported lower anxiety during Months 1 ($M = 5.37$, $SD = 0.92$, $p = .002$), 2 ($M = 6.55$, $SD = 0.96$, $p = .033$), and 3 ($M = 5.96$, $SD = 1.13$, $p = .027$) of CBD consumption relative to baseline ($M = 8.60$, $SD = 1.19$).

Stress

A 2 × 4 mixed ANOVA revealed a main effect of time on DASS-21 stress scores, Greenhouse–Geisser adjusted; $F(2.44, 75.67) = 4.20$, $p = .013$, $\eta_p^2 = 0.12$, observed power = 0.78. Participants reported lower stress during Months 1 ($M = 10.14$, $SD = 1.20$, $p = .046$), 2 ($M = 9.86$, $SD = 1.16$, $p = .054$), and 3 ($M = 8.61$, $SD = 1.12$, $p = .004$) of CBD consumption relative to baseline ($M = 12.67$, $SD = 1.37$). No other effects were observed.

Depression

A 2 × 4 mixed ANOVA revealed no main or interaction effects on DASS-21 depression scores.

Irritability

A 2 × 4 mixed ANOVA revealed a main effect of time on BITe irritability scores, $F(2.01, 62.15) = 3.22$, $p = .047$, $\eta_p^2 = 0.10$, observed power = .60. Participants reported lower irritability during Months 1 ($M = 11.76$, $SD = 0.58$, $p = .042$), 2 ($M = 11.80$, $SD = 0.60$, $p = .076$), and 3 ($M = 11.59$, $SD = 0.62$, $p = .027$) of CBD consumption relative to baseline ($M = 13.52$, $SD = 0.71$).

Discussion

The present study aimed to examine the potential effects of orally ingested CBD isolate for alleviating MRS. Though past work has

Table 5
Descriptive Statistics of Other Health Outcomes by Condition for the 3-Month Sample

Outcome	Month	160 mg (n = 17)			320 mg (n = 16)		
		M	*SD*	(Min, Max)	*M*	*SD*	(Min, Max)
DASS-anxiety	Baseline	8.82	5.66	(0.00, 18.00)	8.38	7.87	(0.00, 20.00)
	Month 1	6.12	5.12	(0.00, 14.00)	4.63	5.40	(0.00, 20.00)
	Month 2	7.53	5.94	(0.00, 20.00)	5.38	5.04	(0.00, 16.00)
	Month 3	7.18	8.49	(0.00, 28.00)	4.75	3.26	(0.00, 32.00)
DASS-depression	Baseline	9.65	6.80	(0.00, 20.00)	8.00	6.61	(0.00, 24.00)
	Month 1	6.24	5.43	(0.00, 18.00)	5.88	5.49	(0.00, 20.00)
	Month 2	7.41	7.20	(0.00, 24.00)	5.75	6.02	(0.00, 18.00)
	Month 3	8.59	9.27	(0.00, 26.00)	7.25	9.18	(0.00, 10.00)
DASS-stress	Baseline	12.59	7.87	(2.00, 28.00)	12.75	7.86	(0.00, 28.00)
	Month 1	9.65	6.13	(2.00, 24.00)	10.63	7.58	(0.00, 30.00)
	Month 2	10.35	5.62	(2.00, 22.00)	9.38	7.61	(0.00, 24.00)
	Month 3	8.35	6.90	(0.00, 22.00)	8.88	5.84	(0.00, 24.00)
BITe-irritability	Baseline	12.53	4.20	(7.00, 23.00)	14.50	3.95	(8.00, 21.00)
	Month 1	10.76	3.09	(6.00, 16.00)	12.75	3.59	(6.00, 20.00)
	Month 2	11.53	3.34	(5.00, 19.00)	12.06	3.53	(5.00, 19.00)
	Month 3	11.24	3.40	(5.00, 17.00)	11.94	3.66	(5.00, 19.00)

Note. DASS = Depression Anxiety Stress Scale; BITe = Brief Irritability Test; Min = minimum; Max = maximum.

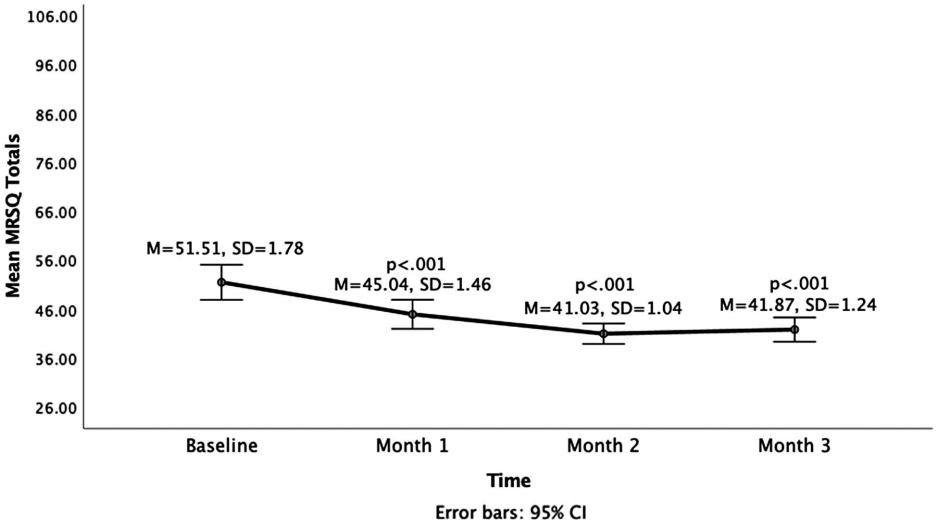
Table 6
Interaction Effects and Main Effects of Dosing Condition for All Outcomes

Outcome	*df* (error-*df*)	*F*	*p*	η_p^2	1 − β
MRSQ total					
Interaction effect	3.00 (29.00)	0.84	.483	0.08	0.21
Main effect of dosing condition	1.00 (31.00)	0.01	.920	0.00	0.05
Subjective severity					
Interaction effect	3.00 (29.00)	0.20	.895	0.02	0.08
Main effect of dosing condition	1.00 (31.00)	0.94	.339	0.03	0.16
Global impression of change					
Interaction effect	3.00 (29.00)	0.45	.717	0.05	0.13
Main effect of dosing condition	1.00 (31.00)	0.17	.687	0.01	0.07
DASS-anxiety					
Interaction effect	3.00 (29.00)	0.33	.803	0.05	0.10
Main effect of dosing condition	1.00 (31.00)	1.62	.217	0.07	0.23
DASS-depression					
Interaction effect	3.00 (29.00)	0.17	.919	0.02	0.08
Main effect of dosing condition	1.00 (31.00)	0.38	.541	0.01	0.09
DASS-stress					
Interaction effect	3.00 (29.00)	0.41	.749	0.04	0.12
Main effect of dosing condition	1.00 (31.00)	0.01	.931	0.00	0.05
BITe-irritability					
Interaction effect	3.00 (29.00)	1.08	.375	0.10	0.26
Main effect of dosing condition	1.00 (31.00)	2.07	.161	0.06	0.29

Note. MRSQ = Menstrual-Related Symptoms Questionnaire; DASS = Depression Anxiety Stress Scale; BITe = Brief Irritability Test.

suggested cannabis may be a viable option for MRS intervention (Hanzal et al., 2019; Joyce et al., 2021; Slavin et al., 2017), to our knowledge, this study is the first to examine the effects of CBD on MRS directly. Results revealed reductions in monthly ratings of MRS (using the MRSQ; $M_{\%change}$ = 17.21), subjective severity of symptoms ($M_{\%change}$ = 19.70), global impression of change ($M_{\%change}$ = 20.92), anxiety ($M_{\%change}$ = 30.70), stress ($M_{\%change}$ = 24.73), and irritability ($M_{\%change}$ = 13.33) in both dosing conditions when comparing Months 1, 2, and 3 of CBD consumption to baseline. Notably, changes in symptoms across primary outcomes (i.e., MRS) appeared in the first month of CBD consumption and persisted consistently across subsequent study months for most

Figure 2
Mean Differences in MRSQ Scores Across All Study Time Points



Note. N = 33. Participants reported reduced MRSQ scores during all 3 consumption months compared to baseline, Greenhouse–Geisser adjusted; $F(2.43, 75.39) = 17.42$, $p < .001$, $\eta_p^2 = 0.36$, observed power = 1.00. Planned contrast analyses for the main effect of time comparing Months 1, 2, and 3 of CBD consumption to baseline are represented with p values and means in the graph. MRSQ scale: 26–104. MRSQ = Menstrual-Related Symptoms Questionnaire.

outcomes (see Table 7). No differential dose effects were observed across any outcomes. Taken together, findings suggest that CBD may help manage MRS and related psychological outcomes.

The present study findings are consistent with past research showing the beneficial effects of CBD on various experiences associated with MRS, including reductions in monthly ratings of MRS (using the MRSQ, subjective severity, global impression of change), stress, and anxiety (Zuardi et al., 2017). Data revealed reductions in both physiological and psychological symptoms, which is consistent with past literature documenting effects of CBD on both types of outcomes (Boyaji et al., 2020; Shannon et al., 2019; Linares et al., 2019; Loflin et al., 2017); however, various physiological symptoms that are assessed in the MRSQ had not been examined in relation to CBD prior to the present investigation (i.e., abdominal bloating, nausea, appetite-related symptoms; Sexton et al., 2016; Slavin et al., 2017) and thus warrant future research and replication.

CBD has been associated with reducing pain related to inflammation (Burstein, 2015). To the extent that some physiological MRS may be a result of inflammation (Barcikowska et al., 2020; Gold et al., 2016), CBD may reduce some pain-related physiological MRS; though this study did not examine anti-inflammatory outcomes, future work may examine the effects of CBD on biological markers of menstrual-related inflammation. Also, consistent with past literature, we observed reductions in anxiety in the 320 mg condition; however, we also found reductions in the 160 mg condition (though trends suggest a small dose effect for some symptoms; Zuardi et al., 2017). The present study is the first to our knowledge to examine the potential effect of CBD on irritability; findings showed a small reduction in irritability symptoms in all 3 months of CBD consumption relative to baseline. When comparing all 3 months of CBD consumption to baseline, on average, participants shifted from mild ratings of depression to reporting in the normal range (Lovibond & Lovibond, 1995).

Table 7
Total Sample Clinical Outcome Changes Across Study Time Points

Outcome	Month	*M*	Clinical range
MRSQ (PR: 26–104)	Baseline	52.65	Second quartile
	Month 1	43.71	First quartile
	Month 2	40.65	First quartile
	Month 3	42.06	First quartile
DASS-anxiety (PR: 0–42)	Baseline	8.82	Mild
	Month 1	6.12	Normal
	Month 2	7.53	Normal
	Month 3	7.18	Normal
DASS-depression (PR: 0–42)	Baseline	9.65	Mild
	Month 1	6.24	Normal
	Month 2	7.41	Normal
	Month 3	8.59	Normal
DASS-stress (PR: 0–42)	Baseline	12.59	Normal
	Month 1	9.65	Normal
	Month 2	10.35	Normal
	Month 3	8.35	Normal
BITe-irritability (PR: 5–30)	Baseline	12.53	Second quartile
	Month 1	10.76	First quartile
	Month 2	11.53	Second quartile
	Month 3	11.24	First quartile

Note. DASS[50] clinical cutoff recommendations are cited in the literature. MRSQ and BITe scores have not been cited in the literature for clinical cutoff recommendations, therefore quartiles were used. Higher scores for all measures indicate greater symptoms. MRSQ = Menstrual-Related Symptoms Questionnaire; DASS = Depression Anxiety Stress Scale; BITe = Brief Irritability Test; PR = plausible range.

Several strengths of the present study should be noted. First, to our knowledge, the present study is the first study to implement a dosing approach for which participants consumed CBD for 5 consecutive days beginning on the first day of MRS for 3 consecutive months. Though dependent on dose, route of administration, and frequency of use, the half-life of CBD may be up to 5 days (Millar et al., 2018), which suggests that the CBD consumed in 1 month of the present study would likely have been largely metabolized by the following study month. Thus, our dosing approach is a series of acute dosing bouts as opposed to chronic dosing approach given the repeated and acute nature of MRS. The dosing paradigm can be leveraged in future studies examining differences in acute versus prolonged dosing of CBD for the management of MRS. Further, this dosing paradigm may be implemented for the management of other temporally variable experiences (e.g., substance craving) that may benefit from an "as needed" CBD dosing approach. Another strength is that we employed well-validated measures to assess MRS and related constructs. Finally, by comparing two different doses, we were able to demonstrate a lack of dose effect (for the tested doses) for some symptoms and a potential mild dose effect for others that warrants further investigation when using CBD for managing MRS.

Though the present study findings provide early evidence for the utility of CBD as an intervention for MRS, various limitations should be noted. First, we used a relatively homogenous sample that potentially oversampled individuals who suffer from moderate severity of MRS. Though having a homogenous sample with regards to MRS reduces potential confounds, CBD may only affect a specific range of symptom severity. Future work might examine clinically relevant samples who may suffer from severe MRS or PMDD to further assess the utility of CBD as a potential strategy for managing more severe MRS. Second, participants were not compensated for this study and to limit participant burden, the present study relied on individuals' self-reported consumption of CBD at prescribed doses and times; future work should consider verification of consumption using more rigorous verification method such as video confirmation of CBD consumption. Future work may also implement video confirmation of a provided high-fat snack to promote the bioavailability of CBD during consumption (Mozaffari et al., 2021; Stott et al., 2013). Third, the present study did not implement a placebo control. Reductions from baseline to intervention months may have resulted from a placebo effect, as various cannabinoid expectancy effects have been documented across a range of symptoms associated with MRS, such as pain, anxiety, and stress (Altman et al., 2021; De Vita et al., 2022; Gertsch, 2018; Spinella et al., 2021). Future work should investigate the efficacy of CBD for MRS relative to placebo as well as controlling for cannabinoid expectancy effects (e.g., controlling for lifetime cannabis use). If expectancy effects influenced responding, the lack of placebo may also account for little-to-no dose effects emerging. A lack of consistently observed dose effects may also be a result of relatively similar doses (compared to some previous literature demonstrating dose effects with 300 mg and 600 mg doses; e.g., Bergamaschi et al., 2011; Linares et al., 2019). A lack of dose effect may also be from possible ceiling effects if 160 mg is enough CBD to influence some outcomes or floor effects if 320 mg is not enough CBD to influence others. Fourth, given the length of the

study, attrition levels were high, and future work may benefit from using incentives to promote retention.

Further, given that the symptom expression of MRS is variable between and among individuals who menstruate, many individuals did not meet the criteria for study inclusion because their cycles did not meet the requirement of experiencing a regular period. Missing cycles and/or irregular periods are common, as many indogenous and exogenous stressors can impact the timing of menstrual cycles (hormonal imbalance, socioeconomic status, pandemic-related stress; Kwak et al., 2019; Ozimek et al., 2022). Future research might examine the effects of CBD on MRS among individuals who experience irregular periods. Last, we did not validate which cycle phases participants were experiencing at any point of the study; further research might examine the utility of CBD for MRS across phases of the menstrual cycle using salivary progesterone concentrations. Future work might also benefit from investigating the administration of CBD combined with other cannabinoids and/or terpenes, varying routes of administration, and/or varying doses to optimize CBD consumption for MRS alleviation. Future work may also examine the utility of CBD on other outcomes similar to MRS experiences (e.g., menopause).

The present study suggests that CBD may be an effective treatment in alleviating MRS. Given the prevalence of MRS as well as the relative lack of effective options in treating the entirety of experiences that occur because of MRS, further investigation of CBD as an intervention option for MRS is warranted. This study provides early evidence for CBD as an option for managing MRS, and more research is needed to further determine the utility and optimize CBD administration for reducing MRS with various possibilities for future directions.

References

Allen, D. (1996). Are alcoholic women more likely to drink premenstrually? *Alcohol and Alcoholism*, *31*(2), 145–147. https://doi.org/10.1093/oxfordjournals.alcalc.a008125

Altman, B. R., Mian, M. N., Ueno, L. F., & Earleywine, M. (2021). Expectancies about the effects of cannabidiol products on anxiety symptoms. *Journal of Substance Use*, *28*(1), 46–52. https://doi.org/10.1080/14659891.2021.2006341

Andreae, M. H., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A., Abrams, D. I., Prasad, H., Wilsey, B., Indyk, D., Johnson, M., & Sacks, H. S. (2015). Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *The Journal of Pain*, *16*(12), 1221–1232. https://doi.org/10.1016/j.jpain.2015.07.009

Barcikowska, Z., Rajkowska-Labon, E., Grzybowska, M. E., Hansdorfer-Korzon, R., & Zorena, K. (2020). Inflammatory markers in dysmenorrhea and therapeutic options. *International Journal of Environmental Research and Public Health*, *17*(4), Article 1191. https://doi.org/10.3390/ijerph17041191

Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., de Oliveira, D. C. G., De Martinis, B. S., Kapczinski, F., Quevedo, J., Roesler, R., Schröder, N., Nardi, A. E., Martín-Santos, R., Hallak, J. E., Zuardi, A. W., & Crippa, J. A. S. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*, *36*(6), 1219–1226. https://doi.org/10.1038/npp.2011.6

Borenstein, J. E., Dean, B. B., Leifke, E., Korner, P., & Yonkers, K. A. (2007). Differences in symptom scores and health outcomes in premenstrual syndrome. *Journal of Women's Health*, *16*(8), 1139–1144. https://doi.org/10.1089/jwh.2006.0230

Boyaji, S., Merkow, J., Elman, R. N. M., Kaye, A. D., Yong, R. J., & Urman, R. D. (2020). The role of cannabidiol (CBD) in chronic pain management: An assessment of current evidence. *Current Pain and Headache Reports*, *24*(2), Article 4. https://doi.org/10.1007/s11916-020-0835-4

Breier, A., Charney, D. S., & Heninger, G. R. (1986). Agoraphobia with panic attacks. Development, diagnostic stability, and course of illness. *Archives of General Psychiatry*, *43*(11), 1029–1036. https://doi.org/10.1001/archpsyc.1986.01800110015003

Burstein, S. (2015). Cannabidiol (CBD) and its analogs: A review of their effects on inflammation. *Bioorganic & Medicinal Chemistry*, *23*(7), 1377–1385. https://doi.org/10.1016/j.bmc.2015.01.059

Cascade, E., Kalali, A. H., & Kennedy, S. H. (2009). Real-world data on SSRI antidepressant side effects. *Psychiatry*, *6*(2), 16–18.

Chesney, M. A., & Tasto, D. L. (1975). The development of the menstrual symptom questionnaire. *Behaviour Research and Therapy*, *13*(4), 237–244. https://doi.org/10.1016/0005-7967(75)90028-5

Cleveland Clinic. (2022). *Menstrual cycle (normal menstruation): Overview & phases*. https://my.clevelandclinic.org/health/articles/10132-menstrual-cycle

Cook, B. L., Noyes, R., Jr., Garvey, M. J., Beach, V., Sobotka, J., & Chaudhry, D. (1990). Anxiety and the menstrual cycle in panic disorder. *Journal of Affective Disorders*, *19*(3), 221–226. https://doi.org/10.1016/0165-0327(90)90095-P

Cook, W. B., & Dallas, G. (2008). Common adverse events and interactions with OTC pain medications. *U. S. Pharmacist*, *33*(5), 44–56.

Creinin, M. D., Keverline, S., & Meyn, L. A. (2004). How regular is regular? An analysis of menstrual cycle regularity. *Contraception*, *70*(4), 289–292. https://doi.org/10.1016/j.contraception.2004.04.012

De Vita, M. J., Maisto, S. A., Gilmour, C. E., McGuire, L., Tarvin, E., & Moskal, D. (2022). The effects of cannabidiol and analgesic expectancies on experimental pain reactivity in healthy adults: A balanced placebo design trial. *Experimental and Clinical Psychopharmacology*, *30*(5), 536–546. https://doi.org/10.1037/pha0000465

Dickerson, L. M., Mazyck, P. J., & Hunter, M. H. (2003). Premenstrual syndrome. *American Family Physician*, *67*(8), 1743–1752.

Dimmock, P. W., Wyatt, K. M., Jones, P. W., & O'Brien, P. M. (2000). Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: A systematic review. *Lancet*, *356*(9236), 1131–1136. https://doi.org/10.1016/S0140-6736(00)02754-9

Direkvand-Moghadam, A., Sayehmiri, K., Delpisheh, A., & Kaikhavandi, S. (2014). Epidemiology of premenstrual syndrome (PMS)-a systematic review and meta-analysis study. *Journal of Clinical and Diagnostic Research*, *8*(2), 106–109. https://doi.org/10.7860/JCDR/2014/8024.4021

Elflein, J. (2023, April 24). *Antidepressant overdose deaths U.S. 1999–2021*. Statista. https://www.statista.com/statistics/895959/antidepressant-overdose-deaths-us/

Evans, E. A., & Sullivan, M. A. (2014). Abuse and misuse of antidepressants. *Substance Abuse and Rehabilitation*, *5*, 107–120. https://doi.org/10.2147/SAR.S37917

Evans, S. M., Haney, M., & Foltin, R. W. (2002). The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. *Psychopharmacology*, *159*(4), 397–406. https://doi.org/10.1007/s00213-001-0944-7

Ferguson, J. M. (2001). SSRI antidepressant medications: Adverse effects and tolerability. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(1), 22–27. https://doi.org/10.4088/PCC.v03n0105

Ferretti, M. L., Stanley, T. B., & Irons, J. G. (2022). Initial validity evidence for the Menstrual-Related Symptoms Questionnaire. *Women's Reproductive Health*, *10*(1), 43–55. https://doi.org/10.1080/23293691.2022.2038522

Gertsch, J. (2018). The intricate influence of the placebo effect on medical cannabis and cannabinoids. *Medical Cannabis and Cannabinoids*, *1*(1), 60–64. https://doi.org/10.1159/000489291

Gold, E. B., Wells, C., & Rasor, M. O. N. (2016). The association of inflammation with premenstrual symptoms. *Journal of Women's Health*, *25*(9), 865–874. https://doi.org/10.1089/jwh.2015.5529

Gonda, X., Telek, T., Juhasz, G., Lazary, J., Vargha, A., & Bagdy, G. (2008). Patterns of mood changes throughout the reproductive cycle in healthy women without premenstrual dysphoric disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(8), 1782–1788. https://doi.org/10.1016/j.pnpbp.2008.07.016

Halbreich, U., Borenstein, J., Pearlstein, T., & Kahn, L. S. (2003). The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology*, *28*(Suppl. 3), 1–23. https://doi.org/10.1016/S0306-4530(03)00098-2

Handy, A. B., Greenfield, S. F., Yonkers, K. A., & Payne, L. A. (2022). Psychiatric symptoms across the menstrual cycle in adult women: A comprehensive review. *Harvard Review of Psychiatry*, *30*(2), 100–117. https://doi.org/10.1097/HRP.0000000000000329

Hanzal, N., Joyce, K. M., Tibbo, P. G., & Stewart, S. H. (2019). A pilot daily diary study of changes in stress and cannabis use quantity across the menstrual cycle. *Cannabis*, *2*(2), 120–134. https://doi.org/10.26828/cannabis.2019.02.002

Holtzman, S., O'Connor, B. P., Barata, P. C., & Stewart, D. E. (2015). The Brief Irritability Test (BITe): A measure of irritability for use among men and women. *Assessment*, *22*(1), 101–115. https://doi.org/10.1177/1073191114533814

Iffland, K., & Grotenhermen, F. (2017). An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. *Cannabis and Cannabinoid Research*, *2*(1), 139–154. https://doi.org/10.1089/can.2016.0034

Joyce, K. M., Thompson, K., Good, K. P., Tibbo, P. G., O'Leary, M. E., Perrot, T. S., Hudson, A., & Stewart, S. H. (2021). The impact of depressed mood and coping motives on cannabis use quantity across the menstrual cycle in those with and without pre-menstrual dysphoric disorder. *Addiction*, *116*(10), 2746–2758. https://doi.org/10.1111/add.15465

Kaspi, S. P., Otto, M. W., Pollack, M. H., Eppinger, S., & Rosenbaum, J. F. (1994). Premenstrual exacerbation of symptoms in women with panic disorder. *Journal of Anxiety Disorders*, *8*(2), 131–138. https://doi.org/10.1016/0887-6185(94)90011-6

Kim, H. Y. (2013). Statistical notes for clinical researchers: Assessing normal distribution (2) using skewness and kurtosis. *Restorative Dentistry & Endodontics*, *38*(1), 52–54. https://doi.org/10.5395/rde.2013.38.1.52

Kornstein, S. G., Harvey, A. T., Rush, A. J., Wisniewski, S. R., Trivedi, M. H., Svikis, D. S., McKenzie, N. D., Bryan, C., & Harley, R. (2005). Self-reported premenstrual exacerbation of depressive symptoms in patients seeking treatment for major depression. *Psychological Medicine*, *35*(5), 683–692. https://doi.org/10.1017/S0033291704004106

Kwak, Y., Kim, Y., & Baek, K. A. (2019). Prevalence of irregular menstruation according to socioeconomic status: A population-based nationwide cross-sectional study. *PLOS ONE*, *14*(3), Article e0214071. https://doi.org/10.1371/journal.pone.0214071

Larsen, C., & Shahinas, J. (2020). Dosage, efficacy and safety of cannabidiol administration in adults: A systematic review of human trials. *Journal of Clinical Medicine Research*, *12*(3), 129–141. https://doi.org/10.14740/jocmr4090

Lester, N. A., Keel, P. K., & Lipson, S. F. (2003). Symptom fluctuation in bulimia nervosa: Relation to menstrual-cycle phase and cortisol levels. *Psychological Medicine*, *33*(1), 51–60. https://doi.org/10.1017/S0033291702006815

Linares, I. M., Zuardi, A. W., Pereira, L. C., Queiroz, R. H., Mechoulam, R., Guimarães, F. S., & Crippa, J. A. (2019). Cannabidiol presents an inverted U-shaped dose–response curve in a simulated public speaking test. *The British Journal of Psychiatry*, *41*(1), 9–14. https://doi.org/10.1590/1516-4446-2017-0015

Loflin, M. J., Babson, K. A., & Bonn-Miller, M. O. (2017). Cannabinoids as therapeutic for PTSD. *Current Opinion in Psychology*, *14*, 78–83. https://doi.org/10.1016/j.copsyc.2016.12.001

Lopez, H. L., Cesareo, K. R., Raub, B., Kedia, A. W., Sandrock, J. E., Kerksick, C. M., & Ziegenfuss, T. N. (2020). Effects of hemp extract on markers of wellness, stress resilience, recovery and clinical biomarkers of safety in overweight, but otherwise healthy subjects. *Journal of Dietary Supplements*, *17*(5), 561–586. https://doi.org/10.1080/19390211.2020.1765941

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy*, *33*(3), 335–343. https://doi.org/10.1016/0005-7967(94)00075-U

Marjoribanks, J., Ayeleke, R. O., Farquhar, C., Proctor, M., & the Cochrane Gynaecology and Fertility Group. (2015). Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database of Systematic Reviews*, *2015*(7), Article CD001751. https://doi.org/10.1002/14651858.CD001751.pub3

Meaden, P. M., Hartlage, S. A., & Cook-Karr, J. (2005). Timing and severity of symptoms associated with the menstrual cycle in a community-based sample in the Midwestern United States. *Psychiatry Research*, *134*(1), 27–36. https://doi.org/10.1016/j.psychres.2005.01.003

Millar, S. A., Stone, N. L., Yates, A. S., & O'Sullivan, S. E. (2018). A systematic review on the pharmacokinetics of cannabidiol in humans. *Frontiers in Pharmacology*, *9*, Article 1365. https://doi.org/10.3389/fphar.2018.01365

Mozaffari, K., Willette, S., Lucker, B. F., Kovar, S. E., Holguin, F. O., & Guzman, I. (2021). The effects of food on cannabidiol bioaccessibility. *Molecules*, *26*(12), Article 3573. https://doi.org/10.3390/molecules26123573

Ozimek, N., Velez, K., Anvari, H., Butler, L., Goldman, K. N., & Woitowich, N. C. (2022). Impact of stress on menstrual cyclicity during the coronavirus disease 2019 pandemic: A survey study. *Journal of Women's Health*, *31*(1), 84–90. https://doi.org/10.1089/jwh.2021.0158

Pearlstein, T., & Steiner, M. (2012). Premenstrual dysphoric disorder: Burden of illness and treatment update. *Focus—American Psychiatric Publishing*, *10*(1), 90–101. https://doi.org/10.1176/appi.focus.10.1.90

Pearlstein, T., Yonkers, K. A., Fayyad, R., & Gillespie, J. A. (2005). Pretreatment pattern of symptom expression in premenstrual dysphoric disorder. *Journal of Affective Disorders*, *85*(3), 275–282. https://doi.org/10.1016/j.jad.2004.10.004

Rasgon, N., Bauer, M., Glenn, T., Elman, S., & Whybrow, P. C. (2003). Menstrual cycle related mood changes in women with bipolar disorder. *Bipolar Disorders*, *5*(1), 48–52. https://doi.org/10.1034/j.1399-5618.2003.00010.x

Reed, S. C., Levin, F. R., & Evans, S. M. (2008). Changes in mood, cognitive performance and appetite in the late luteal and follicular phases of the menstrual cycle in women with and without PMDD (premenstrual dysphoric disorder). *Hormones and Behavior*, *54*(1), 185–193. https://doi.org/10.1016/j.yhbeh.2008.02.018

Russo, E. B., Guy, G. W., & Robson, P. J. (2007). Cannabis, pain, and sleep: Lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chemistry & Biodiversity*, *4*(8), 1729–1743. https://doi.org/10.1002/cbdv.200790150

Russo, E. B., & Hohmann, A. G. (2013). Role of cannabinoids in pain management. In T. Deer, M. S. Leong, A. Buvanendran, V. Gordin, P. S. Kim, S. J. Panchal, & A. L. Ray (Eds.), *Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches* (pp. 181–197). Springer.

Schier, A. R. D. M., Ribeiro, N. P. D. O., Silva, A. C., Hallak, J. E., Crippa, J. A., Nardi, A. E., & Zuardi, A. W. (2012). Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. *The British Journal of Psychiatry*, *34*(Suppl. 1), S104–S110. https://doi.org/10.1016/S1516-4446(12)70057-0

Sexton, M., Cuttler, C., Finnell, J. S., & Mischley, L. K. (2016). A cross-sectional survey of medical cannabis users: Patterns of use and perceived efficacy. *Cannabis and Cannabinoid Research*, *1*(1), 131–138. https://doi.org/10.1089/can.2016.0007

Shannon, S., Lewis, N., Lee, H., & Hughes, S. (2019). Cannabidiol in anxiety and sleep: A large case series. *The Permanente Journal*, *23*(1), 18–041. https://doi.org/10.7812/TPP/18-041

Slavin, M., Barach, E., Farmer, S., Luba, R., & Earleywine, M. (2017). Cannabis and symptoms of PMS and PMDD. *Addiction Research and Theory*, *25*(5), 383–389. https://doi.org/10.1080/16066359.2017.1294165

Spinella, T. C., Stewart, S. H., Naugler, J., Yakovenko, I., & Barrett, S. P. (2021). Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: A randomized crossover study. *Psychopharmacology*, *238*(7), 1965–1977. https://doi.org/10.1007/s00213-021-05823-w

Stott, C. G., White, L., Wright, S., Wilbraham, D., & Guy, G. W. (2013). A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. *European Journal of Clinical Pharmacology*, *69*(4), 825–834. https://doi.org/10.1007/s00228-012-1393-4

Wakil, L., Meltzer-Brody, S., & Girdler, S. (2012). Premenstrual dysphoric disorder: How to alleviate her suffering. *Current Psychiatry*, *11*(4), 22–37.

Wolf, M. S., King, J., Jacobson, K., Di Francesco, L., Bailey, S. C., Mullen, R., McCarthy, D., Serper, M., Davis, T. C., & Parker, R. M. (2012). Risk of unintentional overdose with non-prescription acetaminophen products. *Journal of General Internal Medicine*, *27*(12), 1587–1593. https://doi.org/10.1007/s11606-012-2096-3

Yonkers, K. A., O'Brien, P. M., & Eriksson, E. (2008). Premenstrual syndrome. *Lancet*, *371*(9619), 1200–1210. https://doi.org/10.1016/S0140-6736(08)60527-9

Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimarães, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of Psychopharmacology*, *7*(Suppl. 1), 82–88. https://doi.org/10.1177/026988119300700112

Zuardi, A. W., Crippa, J. A. S., Hallak, J. E., Moreira, F. A., & Guimarães, F. S. (2006). Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Brazilian Journal of Medical and Biological Research*, *39*(4), 421–429. https://doi.org/10.1590/S0100-879X2006000400001

Zuardi, A. W., Rodrigues, N. P., Silva, A. L., Bernardo, S. A., Hallak, J. E. C., Guimarães, F. S., & Crippa, J. A. S. (2017). Inverted U-shaped dose–response curve of the anxiolytic effect of cannabidiol during public speaking in real life. *Frontiers in Pharmacology*, *8*, Article 259. https://doi.org/10.3389/fphar.2017.00259

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