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RESEARCH ARTICLE

The effects of acute versus repeated cannabidiol administration on trauma-relevant emotional reactivity: A double-blind, randomized, placebo-controlled trial

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Abstract

Despite the widespread use and perceived efficacy of cannabidiol (CBD) as an anxiolytic, few controlled studies have evaluated the effects of CBD on anxiety-relevant indications, and only one has done so in the context of trauma-related symptoms. The current study was designed to address this gap in the literature. Participants were 42 trauma-exposed individuals (M_{age} = 23.12 years, SD_{age} = 6.61) who endorsed elevated stress. They were randomly assigned to take 300 mg of oral CBD or placebo daily for 1 week. Acute (i.e., following an initial 300 mg dose) and repeated (i.e., following 1 week of daily 300 mg dosing) effects of CBD were evaluated in relation to indicators of anxious arousal (i.e., anxiety, distress, heart rate) in response to idiographic trauma script presentation. The results of the current study suggest that relative to placebo, 300 mg CBD did not significantly reduce anxiety, B = 13.37, $t(37)$ = 1.71, p = .096, d = 0.09, Bayes factor (BF_{10}) = 0.54; distress, B = 15.20, $t(37)$ = 1.31, p = .197, d = 0.07, BF_{10} = 0.51; or heart rate, B = -1.09, $t(36)$ = -0.32, p = .755, d = 0.02, BF_{10} = 0.29, evoked by idiographic trauma script presentation in the context of acute or repeated administration. These data suggest that CBD may not effectively reduce trauma-relevant emotional arousal; however, more work is needed to confidently assert such claims due to the small sample size. The current study extends the groundwork for additional studies in this important area.

Upwards of 80% of the population will experience a traumatic event in their lifetime (American Psychiatric Association [APA], 2013; Kessler et al., 2017). Although a minority of trauma-exposed individuals go on to develop posttraumatic stress disorder (PTSD; de Vries & Olff, 2009), millions suffer from subthreshold PTSD symptoms (Hruska et al., 2023). Existing treatments, although efficacious can be difficult to access, and dropout is not uncommon (Kehle-Forbes et al., 2016; Racine et al., 2020). To address these concerns, clinicians and researchers have begun exploring alternative treatment options, including plant-based medicines (Rehman et al., 2021).

Data suggest *Cannabis sativa L.* (cannabis), and its intoxicating major constituent Δ9-tetrahydrocannabiniol (Δ9-THC), may reduce trauma-related symptoms (Hill et al., 2022). Nonetheless, the intoxicating nature and legal status of Δ9-THC complicates its widespread adoption in the United States (National Conference of State

Legislatures, 2023). Researchers have, therefore, begun to interrogate other nonintoxicating cannabinoids in the cannabis plant. Cannabidiol (CBD) is one such cannabinoid; unlike Δ9-THC, CBD is legal in the United States if it is derived from cannabis plants containing less than 0.3% Δ9-THC (Agricultural Improvement Act of 2018, 2018). CBD is a favorable alternative to Δ9-THC due to its legal status and robust safety profile (Souza et al., 2022). Theoretical and neurobiological work converges to suggest one of CBD's mechanism of action is its effects on the 5HT1A receptor (Campos & Guimarães, 2008). Human studies have evaluated CBD's effects on anxiety-relevant indications (Berger et al., 2022; Blessing et al., 2015; Crippa et al., 2021; Gournay, Ferretti, et al., 2023; Zuardi et al., 2017) and, to a lesser extent, trauma-related symptoms (Bolsoni et al., 2022; Bonn-Miller et al., 2021). However, the existing literature surrounding CBD's anxiolytic effects is complex and nonuniform.

Two factors are inherent to drawing clear conclusions regarding CBD's efficacy: dosing level (i.e., the quantity administered) and administration schedule (i.e., acute [single] vs. repeated dosing; Leen-Feldner et al., 2021). With regard to dosing level, an acute dose of 300 mg of oral CBD may be the "Goldilocks" dose for beneficial effects, at least for social anxiety (Linares et al., 2019; Zuardi et al., 2017). Indeed, studies suggest that CBD displays an inverted-U dose–response curve in social anxiety elicitation paradigms, such that lower (e.g., 100 mg) and higher (e.g., 900 mg) doses do not yield the effects produced by moderate doses (e.g., 300 mg) when administered acutely to healthy subjects. Complicating the picture, however, is some evidence for null acute effects of moderate doses (e.g., 300 mg) for other types of anxiety (e.g., Kwee et al., 2022), pointing to the continued need to characterize acute CBD effects across anxiety symptom dimensions. Further, given that CBD's effects may be mediated by the serotonin system (e.g., Campos & Guimaraes, 2008), and pharmacokinetic data suggest a buildup of CBD in the system after repeated dosing (Child & Tallon, 2022), there is reason to conjecture that repeated administration of CBD may be more effective than acute administration in reducing anxiety. Indeed, findings support CBD's anxiolytic effects when administered repeatedly among young people with treatment-resistant anxiety (i.e., self-titration up to 800 mg for 12 weeks; Berger et al., 2022), adults with elevated trait worry (i.e., 300 mg vs. placebo for 2 weeks; Gournay, Ferretti, et al., 2023), and teens with social anxiety disorder (300 mg vs. placebo for 4 weeks; Masataka, 2019). A few studies suggest CBD also ameliorates psychological distress, defined as a broad, negatively valenced subjective experience distinguishable from anxiety (Barlow et al., 2002) among individuals reporting elevated levels of COVID-19–distress (320 mg for 1 week; Gournay, Petry, et al., 2023) and health care providers working in a COVID unit (300 mg with standard care vs. standard care alone for 4 weeks; Crippa et al., 2021). Collectively, the extant data suggest CBD's anxiolytic effects vary as a function of dosing level and schedule, although more work is necessary to empirically discern these parameters.

Regarding trauma-related symptoms, at the time of study conceptualization, there were no published studies on the effects of CBD in the context of trauma. Two relevant studies have since been published. Bolsoni and colleagues (2022) explored the acute effects of 300 mg CBD (vs. placebo) on response to idiographic trauma script presentation among individuals with PTSD. Results indicated that, compared to placebo, 300 mg of CBD did not reduce self-reported anxiety, discomfort, heart rate, or blood pressure before, during, or after script presentation. Similar null findings were obtained for repeated ad libitum administration of smoked CBD (Bonn-Miller et al., 2021) and extend a small body of work indicating acute administration of CBD may have relatively limited effects on anxiety other than social anxiety. However, more work is needed with regard to trauma-related symptoms, specifically the extent to which repeated CBD administration reduces reactivity to trauma-relevant scripts. The aim of the current study was to address this gap by conducting a state-of-the-art, multimodal assessment of the acute and repeated effects of 300 mg oral CBD versus placebo administered daily for 1 week on indicators of anxious arousal (i.e., anxiety, distress, heart rate) elicited by idiographic trauma script presentation within a trauma-exposed sample evidencing elevated stress.

Our primary hypotheses were that both acute (i.e., following the initial dose) and repeated (i.e., following 1 week of dosing) CBD administration would reduce anxiety and distress in response to idiographic trauma scripts compared to placebo. In line with empirical work reviewed earlier, we expected that the magnitude of the effect of CBD on anxiety and distress would be greater following repeated administration compared to acute administration. We made a secondary hypothesis that CBD would reduce psychophysiological arousal (i.e., heart rate) compared to placebo following both acute and repeated administration, with larger effects for repeated as compared to acute administration.

METHOD

Participants

Participants were 42 trauma-exposed individuals (M_{age} = 23.12 years, SD_{age} = 6.61) recruited from the community (n = 39) and a university participant pool (n = 3;

see Table 1 for demographic characteristics). We sought to limit floor effects by selecting participants who were likely to evidence some emotional distress to trauma reminders while also limiting the likelihood of excessive reactivity to trauma script presentation. Therefore, eligible participants reported elevated perceived stress, lifetime trauma exposure, and at least one Criterion B symptom (i.e., intrusions), per the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; APA, 2013) PTSD criteria, but did not meet the criteria for full PTSD. Individuals with PTSD were excluded as a conservative effort to ensure participant safety given the effects of CBD in this context had not been tested at study conceptualization. Although this approach does not negate the possibility of creating a ceiling effect, it was not an issue in the current study (see Table 2). Participants also met additional eligibility criteria (Table 3) to ensure participant safety (e.g., not currently pregnant) and eliminate scientific confounds (e.g., no past month CBD use).

Procedure

Interested participants who responded to study advertisements were screened utilizing scripted telephone screening and a semistructured clinical interview for trauma exposure and trauma-related symptoms. Eligible participants were scheduled for the three-phase study protocol (see Figure 1).

Phase I involved an in-laboratory study appointment that began with collecting written informed consent. Female participants confirmed eligibility via a pregnancy test. Participants then completed a baseline survey before collaborating with the principal investigator (PI) to develop idiographic scripts (i.e., one autobiographical neutral script, one index trauma script) per Pitman and colleagues' (1987) widely used and validated script-driven imagery procedures. The neutral and trauma scripts were equated for sensory experiences; however, the trauma script included the most highly rated response propositions participants remembered experiencing during the index (i.e., most distressing) traumatic event identified during the semistructured interview. The PI recorded the scripts. Participants were then administered standardized training in script-driven imagery (Pittman et al., 1987) before self-administering 300 mg CBD or placebo 90 min before script presentation. This allowed for an evaluation of acute CBD effects relative to placebo. Participants then viewed a nature documentary before being equipped with electrodes for physiological measurements. Next, they took part in an idiographic trauma script presentation, which involved the completion of self-report indicators (i.e., Visual Analog Mood Scales [VAMS]; Luria, 1975) before and after script presentation. Participants then engaged in a positive affect induction, were instructed on the procedures, and provided product provisions for Phase II. Phase II involved a week-long administration period in which participants were instructed to take either 300 mg CBD or placebo once daily with food between 8:00 a.m. and 12:00 p.m. and complete an online survey daily between 5:00 p.m. and 7:00 p.m. The administration schedule was selected as pharmacokinetic data suggest steady state (i.e., consistent serum levels) for CBD is rapidly achieved, albeit at twice daily dosing (i.e., within 1 week; Taylor et al., 2018). After the completion of Phase II, participants returned to the lab for Phase III, which allowed for an evaluation of repeated CBD effects relative to placebo. Phase III procedures, including time from investigational product (IP) administration to script presentation, were identical to those in Phase I, sans idiographic trauma script development, as has been done in prior work utilizing laboratory-based anxiety elicitations (Kirschbaum et al., 1995). However, following the positive affect induction, participants completed a poststudy interview to assess side effects they may have experienced during the study, were debriefed, and compensated up to $200 (USD) or the full allotment of course-related research credits for their time.

Participants were randomly assigned to self-administer 300 mg of CBD or placebo at Phase I (acute dose) and once daily for 1 week (repeated dosing). Product was donated by Canopy Growth USA, LLC. Groups were equated in terms of the number of softgels consumed; each day, participants in the 300 mg group took six active 50 mg CBD softgels (i.e., 300 mg of CBD daily), and the placebo group took six inactive placebo softgels. The active group was administered hemp-derived CBD isolate in medium-chain triglyceride (MCT) in the form of 50 mg softgels; the placebo group was administered softgels containing MCT only. Product was manufactured according to current good manufacturing practices and conditions. A third-party laboratory confirmed each capsule exclusively contained 50 mg of CBD and no contaminants. All study procedures were approved by the University of Arkansas's Institutional Review Board.

Measures

Screening measures

Perceived stress

The 10-item Perceived Stress Scale (PSS-10; Cohen & Williamson, 1988) was used to screen for elevated perceived stress (i.e., scores 0.5 standard deviations or more above normed means [16.2]). Participants rated items such as "How often have you felt nervous or stressed?" on a 5-point Likert scale ranging from 0 (*never*) to 4 (*very often*.) The PSS-10 is a psychometrically sound measure

TABLE 1 Sample characteristics, by condition

	Total sample ($N = 42$)		300 mg CBD ($n = 19$)		Placebo ($n = 23$)					
Variable	***M***	***SD***	***M***	***SD***	***M***	***SD***	***t***	***df***	***p***	η^2
Age (years)	23.12	6.61	21.4	4.85	24.4	7.56	2.05	39	.153	.05
BMI (kg/m^2)	25.93	5.02	24.73	5.25	26.93	4.70	1.43	40	.159	.05
VVIQ	2.26	0.95	2.36	1.11	2.17	0.82	−0.64	39	.523	.01
PTSS	39.83	9.56	40.37	10.41	39.39	8.89	−0.46	37	.644	.003
	n	**%**	***n***	**%**	***n***	**%**				
Race							−0.28	39	.778	< .01
White/Caucasian	32	76.2	13	68.4	19	82.6				
Other[a]	10	21.4	5	26.3	4	17.4				
Ethnicity							−0.88	39	.382	.02
Hispanic/Latino/x	7	16.7	2	10.5	5	21.7				
Not Hispanic/Latino/x	34	81.0	16	84.2	18	78.3				
Gender							−0.07	39	.945	< .01
Female	22	40.5	10	52.6	12	52.2				
Male	17	52.4	7	36.8	10	43.5				
Biological sex							0.06	39	.952	<.01
Female	24	57.1	11	57.9	13	56.5				
Male	18	42.9	8	42.1	10	43.5				
Sexual orientation							0.36	39	.723	< .01
Heterosexual/straight	33	78.6	15	79.0	18	78.3				
Other[b]	8	19.0	3	15.8	5	21.7				
Relationship status							0.76	39	.452	.01
Single	25	59.5	11	57.9	14	60.9				
In a relationship	16	38.1	7	36.8	9	39.2				
Educational attainment							2.62	39	.012	.15
High school	21	52.4	13	68.2	9	39.1				
College	11	26.2	3	15.8	10	34.8				
Graduate school	8	19.1	2	10.5	8	26.1				
Annual income (USD)							2.11	39	.041	.10
< $30,000	32	76.2	17	89.5	15	65.2				
> $30,000	9	21.4	1	5.3	8	26.1				
Past–6-month cannabis use[c]							−0.39	26	.703	< .01
Not at all	20	47.6	8	42.1	12	52.2				
Less than once a month	8	19.1	4	21.1	4	17.4				
Past–6-month alcohol use[c]							0.21	34	.832	< .01
Not at all	6	14.3	3	15.8	3	13.0				
Once a month or less	14	33.3	5	16.8	9	39.3				
Once a week or more	10	31.0	6	31.6	7	30.4				
Past–6-month nicotine use[c]							−1.06	17	.303	.06
Not at all	9	21.4	4	21.1	5	21.7				
Once a day or more	8	19.1	4	21.1	4	17.4				
Side effects[d]							−0.83	6	.411	.02
Nausea	1	2.4	1	5.3	0	0.0				
Somnolence	2	4.8	1	5.3	1	5.3				
Increased appetite	2	4.8	1	5.3	1	5.3				
Elevated heart rate	1	2.4	1	5.3	0	0.0				
Anxiety	1	2.4	0	0.0	1	5.3				
Insomnia	1	2.4	1	5.3	0	0.0				

Note: Frequencies and percentages account for the missing data. Demographic variable categories (e.g., transgender) with fewer than five participants were not included to protect identifying information. Sample characteristic data are missing for one participant. CBD = cannabidiol; BMI = body mass index; VVIQ = Vividness of Visual Imagery Questionnaire; PTSS = posttraumatic stress symptoms.

[a]"Other" includes Asian, Black/African American, and multiracial.

[b]"Other" includes gay or lesbian, asexual, and bisexual.

[c]Values will not sum to 100.0% ($N = 42$) due to nonendorsement of drug use.

[d]Six participants reported eight side effects likely related to CBD administration.

TABLE 2 Manipulation check

Variable	*M*	*SD*	*F*	*df*	*p*	η^2_p
	VAMS-A					
Phase I						
Neutral script			10.62	1, 41	.002	.21
Prescript	26.45	17.67				
Postscript	21.52	16.33				
Trauma Script			95.55	1, 41	< .001	.70
Prescript	20.89	15.44				
Postscript	52.07	19.61				
Phase III						
Neutral script			2.95	1, 41	.093	.07
Prescript	19.08	15.19				
Postscript	17.00	12.71				
Trauma Script			70.17	1, 41	< .001	.63
Prescript	18.38	14.84				
Postscript	43.67	19.97				
	VAMS-D					
Phase I						
Neutral script			3.20	1, 41	.090	.07
Prescript	22.95	17.73				
Postscript	19.26	14.70				
Trauma Script			66.99	1, 41	< .001	.62
Prescript	22.05	16.52				
Postscript	51.90	21.51				
Phase III						
Neutral script			3.99	1, 41	.053	.09
Prescript	17.98	17.77				
Postscript	14.29	11.99				
Trauma Script			65.83	1, 41	< .001	.62
Prescript	17.10	14.30				
Postscript	43.74	21.58				
	Heart rate					
Phase I						
Neutral script			0.91	1, 41	.345	.02
Prescript	77.92	12.87				
Postscript	77.37	11.96				
Trauma Script			0.57	1, 41	.453	.01
Prescript	76.98	11.71				
Postscript	76.47	12.06				
Phase III						
Neutral script			1.03	1, 40	.317	.03
Prescript	78.65	10.59				
Postscript	79.32	10.85				
Trauma Script			5.24	1, 40	.027	.12
Prescript	79.06	11.07				
Postscript	77.67	11.35				

Note: VAMS-A = Visual Analog Mood Scale Anxiety; VAM-D = Visual Analog Mood Scale Distress.

TABLE 3 Eligibility criteria

1. Between 18 and 55 years old[a]
2. Body mass index between 18 and 35 kg/m^2
3. Self-report score of ≥ 16.2 on the PSS-10
4. Report lifetime history of *DSM-5*-defined trauma exposure
5. Does not meet the criteria for PTSD
6. No history of significant allergic condition, hypersensitivity, or allergic reactions to snacks provided in the study (i.e., peanut butter, animal crackers, string cheese, or avocado)
7. Not pregnant or currently breastfeeding
8. No history of significant allergic condition, hypersensitivity, or allergic reactions to cannabis, cannabinoid medications, hemp products, medium chain triglyceride oil, or peppermint
9. No past month CBD use
10. No past month use of cannabis or any THC-containing product
11. Willing to abstain from using cannabis or any THC-containing product for the duration of the study
12. Willing to maintain a stable treatment regimen (i.e., no change in current medication use) for the duration of the study
13. Not taking a prescription medication for anxiety
14. Not currently having thoughts of committing suicide
15. Not been diagnosed with bipolar disorder or psychosis
16. No acute illness, such as a respiratory infection or other illness, that would interfere with study participation
17. No history of diagnosis related to liver function and/or significantly impaired liver function (e.g., cirrhosis of the liver, hepatitis)
18. Willing to ensure they have used effective contraception (e.g., oral contraception, double barrier, intrauterine device) for 30 days prior to the study and for 30 days after study completion
19. Access to a ride to the University of Arkansas campus for research appointments
20. Willing to comply with current university mandates as they pertain to COVID-19 protocols (e.g., mask-wearing)
21. Not currently prescribed or taking the following medication: warfarin, clobazam, valproic acid, phenobarbital, mechanistic target of rapamycin (mTOR) inhibitors, oral tacrolimus, St. John's wort, or Epidiolex.

Note: PSS-10 = Perceived Stress Scale-10; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.); PTSD = posttraumatic stress disorder; CBD = cannabidiol; THC = tetrahydrocannabinol.

[a]The upper cutoff for the age range was selected as a conservative approach to ensuring participant safety; because older adults may be more likely to experience adverse events when administering CBD, they were excluded from the study.

(e.g., convergent validity with stress indicators; Cohen & Williamson, 1988). In the current sample, Cronbach's alpha was .89.

Trauma exposure and posttraumatic stress symptoms

The PTSD module of the Diagnostic Interview for Anxiety, Mood, and Obsessive Compulsive and Related Disorders (DIAMOND-PTSD; Tolin et al., 2018) was administered by trained interviewers to assess the inclusion criteria. The DIAMOND is a psychometrically validated (e.g., convergent validity with relevant self-report indices) semistructured interview.

Participant characteristics

Demographic information

A brief demographic questionnaire was administered at screening (i.e., biological sex, age, body mass index [BMI]). Comprehensive demographic characteristics were obtained during Phase I (see Table 1).

Vividness of visual imagery

The Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1973) was utilized to check random assignment with respect to participants' capabilities for visual imagery. The VVIQ is a 16-item measure rated on a 5-point Likert scale ranging from 1 (*perfectly clear and as vivid as normal vision*) to 5 (*no image at all, you only "know" that you are thinking of the object*). The VVIQ is a widely used, psychometrically sound measure (e.g., strong criterion validity; Marks, 1973). In the current sample, Cronbach's alpha was .95.

Protocol compliance

Participants recorded themselves taking the IP via Timestamp, an app that stamps the date and time of the recording (Gournay, Ferretti, et al., 2023). Research staff reviewed these videos to confirm compliance. Noncompliance (i.e., missed doses) was observed in less than 5% of all administrations.

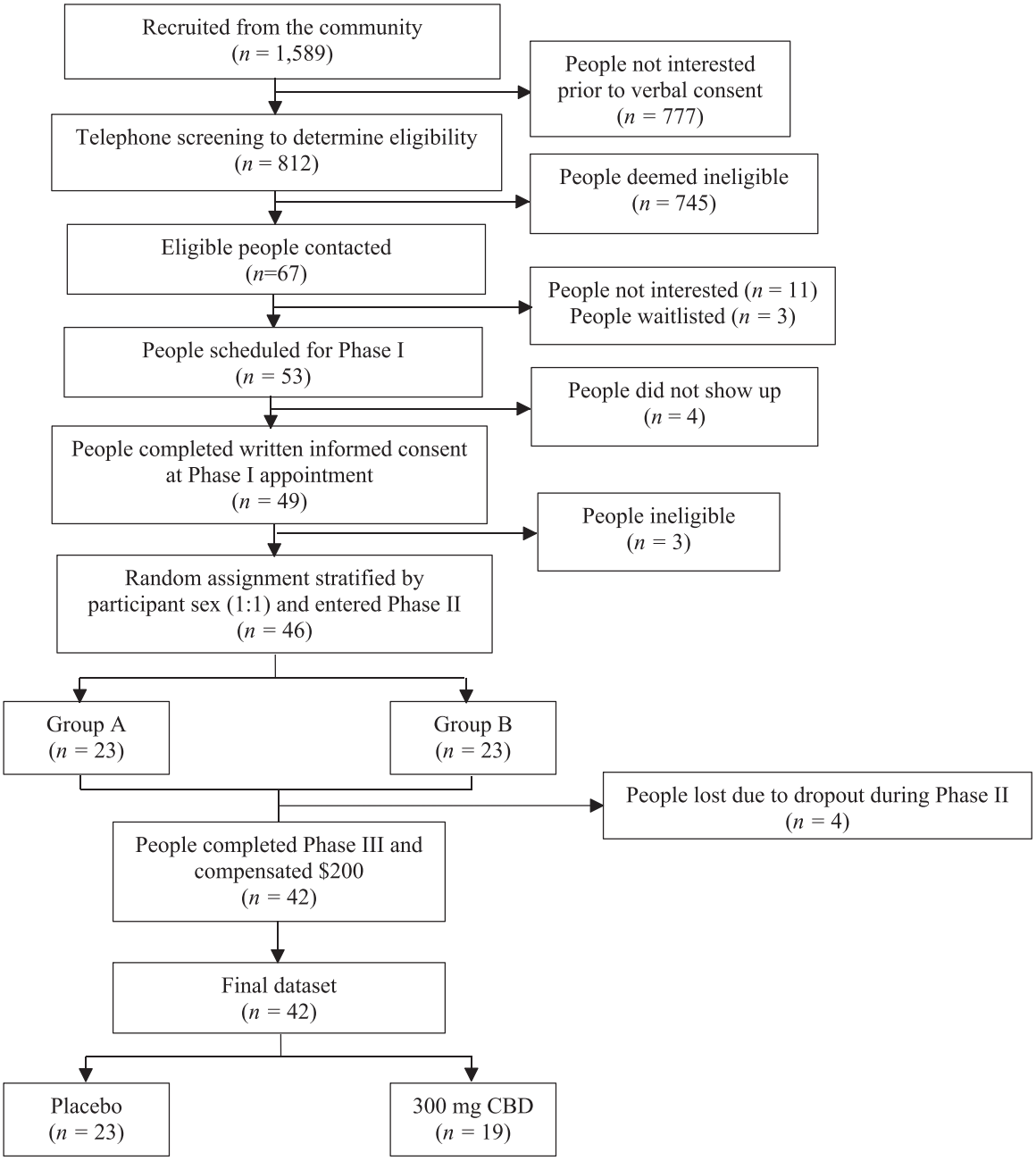

FIGURE 1 Study flow.

Note: For a detailed discussion of participant matriculation and reasons for exclusion, please see the Supplementary Material. CBD = cannabidiol.

Outcome measures

State anxiety

The Anxiety subscale of the VAMS (VAMS-A; Luria, 1975) is a psychometrically validated (e.g., strong convergent validity) index of state anxiety commonly used in cannabinoid administration work (e.g., Bolsoni et al., 2022). Set initially to the middle of the scale, participants used a 100-point sliding scale to rate their current experience for each of three items (e.g., Tranquil–Troubled). Items were averaged to yield an index of state anxiety. In the current sample, Cronbach's alpha values ranged from .88 to .94 across study phases.

Distress

Using the approach described for state anxiety, a single item was used to index distress (VAMS-D), as has been done in prior work (Gournay, Petry, et al., 2023).

Heart rate

A BIOPAC MP 150 data acquisition system (BIOPAC Systems Inc., n.d.) and AcqKnowledge (Version 5.0.6) software were used to obtain electrocardiogram data using

a single-channel biopotential electrocardiogram amplifier (ECG100C). Consistent with recommended guidelines, participants were fitted with disposable Ag/AgCl electrodes placed just below the lower left rib and right collar bone and just above the right ankle (Berntson et al., 2007). Electrocardiogram data were continuously collected during the experimental protocol, and average heart rate in the 30 s epoch before and after the trauma script presentation was used in analyses.

Data analysis

Power analyses were based on the broader literature evaluating the anxiolytic effects of CBD (e.g., Bergamaschi et al., 2011; Masataka, 2019), which suggests a medium-to-large effect size. Using a moderate estimate for effect size (i.e., $d = 0.5$), G*Power statistics software indicated a total of 42 participants ($n = 21$ per condition) were needed to detect effects if present in a repeated-measures design, a sample size that is consistent with similar past work (e.g., Bergamashi et al., 2011).

Inspection of the data revealed no violations of assumptions. Descriptive statistics were computed for all variables at Phase I and Phase III. In line with Bolsoni and colleagues (2022), analyses were relegated to trauma script responses. A manipulation check was conducted to ensure the trauma script presentation increased anxious arousal at Phase I and Phase III. The current study employed a between–within study design such that the levels of the condition factor (300 mg CBD vs. placebo) were compared between participants, and the levels of the script type (neutral vs. trauma), script reactivity (prescript vs. postscript), and study phase (Phase I vs. Phase III) were compared within participants. This approach allowed for an evaluation of the acute (Phase I) and repeated (Phase III) effects of condition on the dependent variables while accounting for script reactivity across script type and study phase. Repeated-measures analysis of variance (ANOVA) models were fit using the *aov_4* function in the *afex* package of R (Version 1.3–1) to estimate the Condition x Script Type x Script Reactivity x Study Phase interaction for all outcome variables (i.e., VAMS-A, VAMS-D, and heart rate) across the administration period (Singmann et al., 2024). Baseline characteristics with significant group differences (i.e., income level and educational attainment) were included as covariates in all models. Inspection of models revealed no violations of assumptions. Bayesian analyses were conducted using the *lmBF* function in the *BayesFactor* package of R (Version 0.9.12–4.7) to produce Bayes factors (BF_{10}) providing evidence for or against the alternative hypothesis. A BF_{10} value greater than 1.0 indicates evidence in favor of the alternative hypothesis, and a BF_{10} value less than 1.0 indicates evidence in favor of the null hypothesis. By convention, BF_{10} values between 0.33 and 3.0 are considered "inconclusive" (Morey & Rouder, 2024). Both *afex* and *lmBF* accounted for individual-level variability. Two unaffiliated collaborators independently replicated all analyses.

RESULTS

Descriptive statistics

The sample was representative of the surrounding locale (see Table 1). Most participants identified as White/Caucasian and heterosexual/straight and reported having completed at least some higher education. Tests for random assignment efficacy revealed no significant differences between condition for VVIQ scores, posttraumatic stress symptoms (PTSS), and most demographic variables; however, participants in the CBD condition reported significantly higher levels of educational attainment, $t(39) = 2.62$, $p = .012$, $\eta^2 = .15$, and higher annual income, $t(39), = 2.11$, $p = .041$, $\eta^2 = .10$, than those in the placebo condition.

Manipulation check

Supporting the efficacy of the manipulation, there were significant increases in VAMS-A and VAMS-D from pre– to post–trauma script presentation at Phase I and Phase III. There were no effects of trauma script presentation on heart rate; however, heart rate at Phase III significantly decreased from pre– to post–trauma script presentation. Table 3 includes descriptive statistics for the manipulation check.

Primary analyses

Anxiety

Participant income, $F(1, 37) = 0.18$, $p = .675$, $\eta^2_p = .005$, and educational attainment, $F(1, 37) = 0.20$, $p = .660$, $\eta^2_p = .005$, were not significant predictors in the model. There was not a significant main effect of condition for VAMS-A, $F(1, 37) = 0.68$, $p = .414$, $\eta^2_p = .02$. However, there were significant main effects of script type, $F(1, 37) = 77.27$, $p < .001$, $\eta^2_p = .71$; script reactivity, $F(1, 37) = 87.05$, $p < .001$, $\eta^2_p = .70$; and study phase, $F(1, 37) = 7.38$, $p = .010$, $\eta^2_p = .17$. There was not a significant Condition x Script Type x Script Reactivity x Study Phase interaction, $F(1, 37) = 2.92$, $p = .096$, $\eta^2_p = .07$. Post hoc slope comparisons (see Table 4) revealed significantly more script reactivity between trauma and neutral script reactivity in Phase I

TABLE 4 Post hoc slope comparisons for the Visual Analog Mood Scale–Anxiety (VAMS-A), Visual Analog Mood Scale–Distress (VAM-D), and heart rate

	Phase I		Phase III							
Variable	***EMM***	***SE***	***EMM***	***SE***	***B***	***t***	***df***	***p***	η^2_p	BF_{10}
VAMS-A					13.37	1.71	37	.096	.04	0.54
CBD					17.35	3.09	37	.004	.08	2.90
Neutral script										
Prescript	27.18	4.33	14.16	3.76						
Postscript	21.51	3.78	15.46	3.19						
Trauma script										
Prescript	19.43	3.62	16.121	3.8						
Postscript	50.26	5.03	36.58	4.96						
Placebo					3.98	0.81	37	.423	0.02	0.33
Neutral Script										
Prescript	24.43	3.78	22.09	3.29						
Postscript	19.72	3.30	17.35	2.78						
Trauma script										
Prescript	20.19	3.17	19.66	3.33						
Postscript	54.36	4.40	49.82	4.33						
VAMS-D					15.20	1.31	37	.197	0.03	0.51
CBD					12.31	1.48	37	.147	0.04	0.75
Neutral script										
Prescript	21.29	4.36	12.30	4.49						
Postscript	16.42	3.31	13.16	3.05						
Trauma script										
Prescript	22.50	4.03	15.97	3.66						
Postscript	49.35	5.58	36.25	5.36						
Placebo					−2.89	−0.40	37	.693	0.01	0.30
Neutral Script										
Prescript	22.64	3.81	21.98	3.92						
Postscript	19.72	2.90	14.48	2.66						
Trauma script										
Prescript	20.04	3.52	17.41	3.20						
Postscript	54.38	4.88	50.06	4.68						
Heart Rate					−1.09	−0.32	36	.755	0.01	0.32
CBD					1.43	0.58	36	.564	0.02	0.25
Neutral script										
Prescript	75.28	3.35	78.65	2.68						
Postscript	75.42	3.11	79.63	2.74						
Trauma script										
Prescript	76.11	3.04	79.47	2.84						
Postscript	74.55	3.12	77.31	2.93						
Placebo					2.52	1.15	36	.258	0.03	0.37
Neutral Script										
Prescript	79.14	3.00	79.23	2.39						
Postscript	78.04	2.78	79.58	2.45						
Trauma script										
Prescript	76.66	2.72	79.25	2.54						
Postscript	76.97	2.79	78.49	2.62						

Note: EMM = estimated marginal mean; BF_{10} = Bayes factor; CBD = cannabidiol.

compared to Phase III within the CBD condition; however, there were no significant differences between trauma and neutral script reactivity across Phase I to Phase III within the placebo condition and no significant differences between trauma and neutral script reactivity across Phase I to Phase III in the CBD condition compared to the placebo condition.

Distress

Participant income, $F(1, 37) = 0.52$, $p = .476$, $\eta^2_p = .01$, and educational attainment, $F(1, 37) = 0.12$, $p = .727$, $\eta^2_p = .003$, were not significant predictors in the model. There was not a significant main effect of condition, $F(1, 37) = 1.03$, $p = .316$, $\eta^2_p = .03$, for the VAMS-D. However, there were significant main effects of script type, $F(1, 37) = 108.70$, $p < .001$, $\eta^2_p = .72$; script reactivity, $F(1, 37) = 61.60$, $p < .001$, $\eta^2_p = .62$; and study phase, $F(1, 37) = 7.40$, $p = .010$, $\eta^2_p = .17$. There was not a significant Condition x Script Type x Script Reactivity x Study Phase interaction, $F(1, 37) = 1.73$, $p = .197$, $\eta^2_p = .04$. Post hoc slope comparisons (see Table 4) revealed no significant differences between trauma and neutral script reactivity across Phase I to Phase III within the CBD condition or placebo condition and no significant differences between trauma and neutral script reactivity across Phase I to Phase III in the CBD condition compared to the placebo condition.

Heart rate

Participant income, $F(1, 36) = 0.01$, $p = .908$, $\eta^2_p = .0004$, and educational attainment, $F(1, 36) = 0.44$, $p = .514$, $\eta^2_p = .01$, were not significant predictors in the model. There were not significant main effects of condition, $F(1, 36) = 0.13$, $p = .723$, $\eta^2_p = .004$; script type, $F(1, 36) = 2.60$, $p = .115$, $\eta^2_p = .19$; script reactivity, $F(1, 36) = 3.30$, $p = .078$, $\eta^2_p = .08$; or study phase, $F(1, 36) = 3.52$, $p = .069$, $\eta^2_p = .09$, for heart rate. There was not a significant Condition x Script Type x Script Reactivity x Study Phase interaction, $F(1, 36) = 0.10$, $p = .755$, $\eta^2_p = .003$. Post hoc slope comparisons (see Table 4) revealed no significant differences between trauma and neutral script reactivity across Phase I to Phase III within the CBD condition or placebo condition and no significant differences between trauma and neutral script reactivity across Phase I to Phase III in the CBD condition compared to the placebo condition.

DISCUSSION

Millions of individuals suffer from subthreshold PTSD symptoms (Hruska et al., 2023). Recent work suggests that CBD has therapeutic potential in the context of anxiety (Blessing et al., 2015) and psychological distress (Crippa et al., 2021). However, only two studies have examined the effects of CBD on trauma-related symptoms, one of which tested an acute 300 mg oral dose of CBD (Bolsoni et al., 2022; Bonn-Miller et al., 2021). Neither found an effect for CBD. Building on this research, the results of the current study suggest that 300 mg CBD did not significantly reduce anxiety, distress, or heart rate evoked by idiographic trauma script presentation in the context of acute or repeated administration compared to placebo.

Unexpectedly, no acute effect of 300 mg CBD (i.e., following the initial dose in Phase I) was obtained for anxiety or distress. However, in the time since the current study hypotheses were formulated, evidence increasingly suggests that CBD's acute anxiolytic effects may be constrained to social anxiety (e.g., Linares et al., 2019), as null effects have emerged for other anxiety-related outcomes (e.g., worry, fear, anxiety after trauma recall; Bolsoni et al., 2022; Gournay, Ferretti, et al., 2023; Kwee et al., 2022; Leen-Feldner et al., 2022). Further, prior work suggesting anxiolytic effects of acute administration of 300 mg CBD was conducted with healthy participants; discrepant findings in the current study, which included participants with elevated PTSS and stress, may be attributable to an interplay between dosing level and psychological vulnerability status. Given that CBD exerts effects, at least in part, via the serotonin system (Campos & Guimaraes, 2008), and disruptions to this system are apparent in participants with subclinical anxiety (e.g., Cerasa et al., 2014), it is plausible that higher doses of CBD and/or longer durations of administration are needed to impact serotonergic activity enough to observe anxiolytic effects.

Similarly, no repeated effects for anxiety or distress were obtained. Notably, these findings contradict work that suggests large beneficial effects of repeated administration of CBD on anxiety (e.g., Crippa et al., 2021; Masataka, 2019). Incongruities may be attributable to expectancy effects, which are potent in cannabinoid administration research (Spinella et al., 2021). The current, double-blind randomized controlled trial (RCT) provides a robust test of the study hypotheses and, given the trends observed in prior work, the absence of significant effects may be due to a placebo response. Although RCTs remain the gold standard, future work could usefully employ placebo effect reduction strategies (e.g., neutral protocol scripts describing treatment; Katz, 2021). Additionally, the divergence in findings between the current study and the only other relevant prospective RCT (Masataka, 2019) may be a result of different dosing durations. The current dosing scheme was selected for pragmatic reasons (e.g., to provide preliminary data evaluating relatively brief repeated dosing intervals) and because the limited human research in this area suggests steady state (i.e., consistent serum levels)

for CBD is rapidly achieved, albeit with twice daily dosing (Taylor et al., 2018). Further, significant reductions in anxiety-related outcomes have been observed after 1 week of CBD administration (e.g., Gournay, Petry, et al., 2023). Masataka (2019) reported reductions in social anxiety after 4 weeks of CBD administration compared to placebo. Relatedly, participants may have habituated to trauma script presentation across sessions; extending the time between elicitation procedures may reduce habituation (Boyle et al., 2016). Moreover, simple effects tests revealed larger effects after repeated administration, suggesting a longer duration could be necessary to attenuate trauma script–driven anxiety and distress. Empirical assessment of dosing duration remains a pressing issue in the CBD literature; the current study meaningfully contributes to this small research base. Finally, a priori simulation-based power analyses were not conducted, leaving open the real possibility that the current analyses may have been underpowered given the discrepancy between the power analysis and data analysis. This idea is supported by the fact that several "inconclusive" Bayes factors were observed and underscores the need for additional larger studies in this area. Also explored were the effects of acute and repeated CBD administration on heart rate. Data regarding CBD's cardiovascular effects are mixed; a recent meta-analysis suggested that CBD influences hemodynamics under conditions of stress but called for more work in the area (Sultan et al., 2017). The current findings accorded with prior work using anxiety-relevant elicitations (e.g., Bolsoni et al., 2022), suggesting CBD does not affect heart rate in this context. Notably, discordant findings between self-reported and psychophysiological indicators are not uncommon. Although trauma script presentation typically increases heart rate in clinical samples (e.g., Pitman et al., 1987), relatively few studies have included nonclinical samples. The lack of heart rate response in the current study fits with the limited work among nonclinical samples in which the presentation of idiographic trauma scripts did not increase heart rate (e.g., Suendermann et al., 2010). A useful next step would be to extend this work to include other physiological indicators of the stress response (e.g., salivary cortisol, alpha amylase).

Despite a number of strengths, including the double-blind design; administration of a validated, laboratory-based experimental psychopathology paradigm; and collection of both subjective and objective indicators of emotional arousal, it merits mention that participants were not diagnosed with PTSD. Additionally, although anxiety was assessed using the VAMS-A to allow comparisons with prior work (e.g., Linares et al., 2019), VAMS items lack face validity (e.g., tranquil vs. troubled). The use of a validated, multi-item assessment (e.g., the State-Trait Anxiety Inventory; Spielberger et al., 1983) would meaningfully extend the current findings. Finally, an objective assessment of participants' compliance with instructions not to use THC during the study would strengthen confidence in the findings.

The current results suggest that neither acute nor repeated administration of 300 mg CBD significantly affected response to an idiographic trauma script presentation relative to placebo. These data suggest that CBD may not effectively reduce trauma-relevant emotional arousal; however, more work is needed to confidently assert such claims.

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OPEN PRACTICES STATEMENT

This study was pre-registered via Open Science Framework (https://osf.io/nxvbe/?view_only=ed4e4a478e9a4d4faa743677b122894a). Requests for deidentified data or materials should be sent via email to the lead author at lrgourna@uark.edu.

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REFERENCES

Agricultural Improvement Act of 2018, H.R. 2, Public Law 115–334, 115th Cong. (2018). https://www.congress.gov/115/plaws/publ334/PLAW-115publ334.pdf

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Barlow, D. H., Raffa, S. D., & Cohen, E. M. (2002). Psychosocial treatments for panic disorders, phobias, and generalized anxiety disorder. In P. E. Nathan & J. M. Gorman (Eds.), *A guide to treatments that work* (pp. 301–335). Oxford University Press.

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. C., 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

Berger, M., Li, E., Rice, S., Davey, C. G., Ratheesh, A., Adams, S., Jackson, H., Hetrick, S., Parker, A., Spelman, T., Kevin, R., McGregor, I. S., McGorry, P., & Amminger, G. P. (2022). Cannabidiol for treatment-resistant anxiety disorders in young people: An open-label trial. *Journal of Clinical Psychiatry*, *83*(5), Article 21m14130. https://doi.org/10.4088/jcp.21m14130

Berntson, G. G., Quigley, K. S., & Lozano, D. (2007). Cardiovascular psychophysiology. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (pp. 182–210). Cambridge University Press.

BIOPAC Systems Inc. (n.d.) *Data acquisition, loggers, amplifiers, transducers, electrodes* [Apparatus and software]. https://www.biopac.com/

Blessing, E. M., Steenkamp, M. M., Manzanares, J., & Marmar, C. R. (2015). Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics*, *12*(4), 825–836. https://doi.org/10.1007/s13311-015-0387-1

Bolsoni, L. M., Crippa, J. A. S., Hallak, J. E. C., Guimarães, F. S., & Zuardi, A. W. (2022). Effects of cannabidiol on symptoms induced by the recall of traumatic events in patients with posttraumatic stress disorder. *Psychopharmacology*, *239*(5), 1499–1507. https://doi.org/10.1007/s00213-021-06043-y

Bonn-Miller, M. O., Sisley, S., Riggs, P., Yazar-Klosinski, B., Wang, J. B., Loflin, M. J. E., Shechet, B., Hennigan, C., Matthews, R., Emerson, A., & Doblin, R. (2021). The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial. *PLOS ONE*, *16*(3), Article e0246990. https://doi.org/10.1371/journal.pone.0246990

Boyle, N. B., Lawton, C., Arkbåge, K., West, S. G., Thorell, L., Hofman, D., Weeks, A., Myrissa, K., Croden, F., & Dye, L. (2016). Stress responses to repeated exposure to a combined physical and social evaluative laboratory stressor in young healthy males. *Psychoneuroendocrinology*, *63*, 119–127. https://doi.org/10.1016/j.psyneuen.2015.09.025

Campos, A. C., & Guimarães, F. S. (2008). Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology*, *199*(2), 223–230. https://doi.org/10.1007/s00213-008-1168-x

Cerasa, A., Quattrone, A., Piras, F., Mangone, G., Magariello, A., Fagioli, S., Girardi, P., Muglia, M., Caltagirone, C., & Spalletta, G. (2014). 5-HTTLPR, anxiety and gender interaction moderates right amygdala volume in healthy subjects. *Social Cognitive and Affective Neuroscience*, *9*(10), 1537–1545. https://doi.org/10.1093/scan/nst144

Child, R. B., & Tallon, M. J. (2022). Cannabidiol (CBD) dosing: Plasma pharmacokinetics and effects on accumulation in skeletal muscle, liver and adipose tissue. *Nutrients*, *14*(10), Article 2101. https://doi.org/10.3390/nu14102101

Cohen, S., & Williamson, G. M. (1988). Perceived stress in a probability sample of the United States. In S. Spaceman & S. Oskamp (Eds.), *The social psychology of health* (pp. 31–67). SAGE.

Crippa, J. A. S., Zuardi, A. W., Guimarães, F. S., Campos, A. C., de Lima Osório, F., Loureiro, S. R., dos Santos, R. G., Souza, J. D. S., Ushirohira, J. M., Pacheco, J. C., Ferreira, R. R., Mancini Costa, K. C., Scomparin, D. S., Scarante, F. F., Pires-Dos-Santos, I., Mechoulam, R., Kapczinski, F., Fonseca, B. A. L., Esposito, D. L. A., … Hallak, J. E. C. (2021). Efficacy and safety of cannabidiol plus standard care vs standard care alone for the treatment of emotional exhaustion and burnout among frontline health care workers during the COVID-19 pandemic: A randomized clinical trial. *JAMA Network Open*, *4*(8), Article e2120603. https://doi.org/10.1001/jamanetworkopen.2021.20603

de Vries, G. J., & Olff, M. (2009). The lifetime prevalence of traumatic events and posttraumatic stress disorder in the Netherlands. *Journal of Traumatic Stress*, *22*(4), 259–267. https://doi.org/10.1002/jts.20429

Gournay, L. R., Ferretti, M. L., Bilsky, S., Vance, E., Nguyen, A. M., Mann, E., Williams, P., & Leen-Feldner, E. W. (2023). The effects of cannabidiol on worry and anxiety among high trait worriers: A double-blind, randomized placebo controlled trial. *Psychopharmacology*, *240*(10), 2147–2161. https://doi.org/10.1007/s00213-023-06437-0

Gournay, L. R., Petry, J., Bynion, T. M., Feldner, M. T., Bonn-Miller, M. O., & Leen-Feldner, E. W. (2023). A multiple baseline study of the effects of cannabidiol on daily perceived stress among people experiencing high levels of COVID distress. *Journal of Endocannabinoid Medicine*, *1*(4).

Hill, M. L., Loflin, M., Nichter, B., Na, P. J., Herzog, S., Norman, S. B., & Pietrzak, R. H. (2022). Cannabis use among U.S. military veterans with subthreshold or threshold posttraumatic stress disorder: Psychiatric comorbidities, functioning, and strategies for coping with posttraumatic stress symptoms. *Journal of Traumatic Stress*, *35*(4), 1154–1166. https://doi.org/10.1002/jts.22823

Hruska, B., Patterson, P. D., Doshi, A. A., Guyette, M. K., Wong, A. H., Chang, B. P., Suffoletto, B. P., & Pacella-LaBarbara, M. L. (2023). Examining the prevalence and health impairment associated with subthreshold PTSD symptoms (PTSS) among frontline healthcare workers during the COVID-19 pandemic. *Journal of Psychiatric Research*, *158*, 202–208. https://doi.org/10.1016/j.jpsychires.2022.12.045

Katz, N. (2021). Design and conduct of confirmatory chronic pain clinical trials. *Pain Reports*, *6*(1), Article e845. https://doi.org/10.1097/pr9.0000000000000854

Kehle-Forbes, S. M., Meis, L. A., Spoont, M. R., & Polusny, M. A. (2016). Treatment initiation and dropout from prolonged exposure and cognitive processing therapy in a VA outpatient clinic. *Psychological Trauma: Theory, Research, Practice, and Policy*, *8*(1), 107–114. https://doi.org/10.1037/tra0000065

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E. J., Cardoso, G., Degenhardt, L., de Girolamo, G., Dinolova, R. V., Ferry, F., Florescu, S., Gureje, O., Haro, J. M., Huang, Y., Karam, E. G., Kawakami, N., Lee, S., Lepine, J. P., Levinson, D., … Koenen, K. C. (2017). Trauma and PTSD in the WHO World Mental Health Surveys. *European Journal of Psychotraumatology*, *8*(supp5), Article 1353383. https://doi.org/10.1080/20008198.2017.1353383

Kirschbaum, C., Pirke, K., & Hellhammer, D. H. (1995). Preliminary evidence for reduced cortisol responsivity to psychological stress in women using oral contraceptive medication. *Psychoneuroendocrinology*, *20*(5), 509–514. https://doi.org/10.1016/0306-4530(94)00078-O

Kwee, C. M., Baas, J. M., van der Flier, F. E., Groenink, L., Duits, P., Eikelenboom, M., van der Veen, D. C., Moerbeek, M., Batelaan, N.

M., van Balkom, A. J., & Cath, D. C. (2022). Cannabidiol enhancement of exposure therapy in treatment-refractory patients with social anxiety disorder and panic disorder with agoraphobia: A randomised controlled trial. *European Neuropsychopharmacology*, *59*, 58–67. https://doi.org/10.1016/j.euroneuro.2022.04.003

Leen-Feldner, E. W., Bynion, T. M., Eglit, G. M. L., Bonn-Miller, M. O., Gournay, L. R., & Feldner, M. T. (2022). A double-blind, randomized, placebo-controlled test of the effects of cannabidiol on fear elicited by a 10% carbon dioxide-enriched air breathing challenge. *Psychopharmacology*, Advance online publication. https://doi.org/10.1007/s00213-022-06258-7

Leen-Feldner, E. W., Bynion, T. M., Gournay, R., Bonn-Miller, M. O., & Feldner, M. T. (2021). Practical considerations for testing the effects of cannabidiol on human anxiety. *Journal of Anxiety Disorders*, *82*, Article 102429. https://doi.org/10.1016/j.janxdis.2021.102429

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. *Revista Brasileira de Psiquiatria*, *41*(1), 9–14. https://doi.org/10.1590/1516-4446-2017-0015

Luria, R. E. (1975). The validity and reliability of the Visual Analogue Mood Scale. *Journal of Psychiatric Research*, *12*(1), 51–57. https://doi.org/10.1016/0022-3956(75)90020-5

Marks, D. F. (1973). Visual imagery differences in the recall of pictures. *British Journal of Psychology*, *64*(1), 17–24. https://doi.org/10.1111/j.2044-8295.1973.tb01322.x

Masataka, N. (2019). Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. *Frontiers in Psychology*, *10*, Article 2466. https://doi.org/10.3389/fpsyg.2019.02466

Morey, R., & Rouder, J. (2024). *BayesFactor: computation of Bayes factors for common designs* (R package Version 0.9.12–4.7) [Computer software]. https://CRAN.R-project.org/package=BayesFactor

National Conference of State Legislatures. (2023). *State medical cannabis laws*. https://www.ncsl.org/health/state-medical-cannabis-laws

Pitman, R. K., Orr, S. P., Forgue, D. F., de Jong, J. B., & Claiborn, J. M. (1987). Psychophysiological assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Archives of General Psychiatry*, *44*(11), 970–975. https://doi.org/10.1001/archpsyc.1987.01800230050009

Racine, N., Hartwick, C., Collin-Vézina, D., & Madigan, S. (2020). Telemental health for child trauma treatment during and post-COVID-19: Limitations and considerations. *Child Abuse & Neglect*, *110*(Pt 2), Article 104698. https://doi.org/10.1016/j.chiabu.2020.104698

Rehman, Y., Saini, A., Huang, S., Sood, E., Gill, R., & Yanikomeroglu, S. (2021). Cannabis in the management of PTSD: A systematic review. *AIMS Neuroscience*, *8*(3), 414–434. https://doi.org/10.3934/neuroscience.2021022

Singmann, H., Bolker, B., Westfall, J., Aust, F., & Ben-Shachar, M. (2024). *afex*: *Analysis of factorial experiments* (R package Version 1.3–1) [Computer software]. https://CRAN.R-project.org/package=afex

Souza, J. D. R., Pacheco, J. C., Rossi, G. N., de-Paulo, B. O., Zuardi, A. W., Guimarães, F. S., Hallak, J. E. C., Crippa, J. A., & dos Santos, R. G. (2022). Adverse effects of oral cannabidiol: An updated systematic review of randomized controlled trials (2020–2022). *Pharmaceutics*, *14*(12), Article 2598. https://doi.org/10.3390/pharmaceutics14122598

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press.

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

Suendermann, O., Ehlers, A., Boellinghaus, I., Gamer, M., & Glucksman, E. (2010). Early heart rate responses to standardized trauma-related pictures predict posttraumatic stress disorder: A prospective study. *Psychosomatic Medicine*, *72*(3), 301–308. https://doi.org/10.1097/PSY.0b013e3181d07db8

Sultan, S. R., Millar, S. A., England, T. J., & O'Sullivan, S. E. (2017). A Systematic Review and Meta-Analysis of the Haemodynamic Effects of Cannabidiol. *Frontiers in Pharmacology*, *8*. https://doi.org/10.3389/fphar.2017.00081

Taylor, L., Gidal, B., Blakey, G., Tayo, B., & Morrison, G. (2018). A Phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects. *CNS Drugs*, *32*(11), 1053–1067. https://doi.org/10.1007/s40263-018-0578-5

Tolin, D. F., Gilliam, C., Wootton, B. M., Bowe, W., Bragdon, L. B., Davis, E., Hannan, S. E., Steinman, S. A., Worden, B., & Hallion, L. S. (2018). Psychometric properties of a structured diagnostic interview for *DSM-5* anxiety, mood, and obsessive–compulsive and related disorders. *Assessment*, *25*(1), 3–13. https://doi.org/10.1177/1073191116638410

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

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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