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ORIGINAL ARTICLE

The anxiolytic effect of cannabidiol depends on the nature of the trauma when patients with post-traumatic stress disorder recall their trigger event

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Objectives: We assessed whether administering cannabidiol (CBD) before recalling the traumatic event that triggered their disorder attenuates anxiety in patients with post-traumatic stress disorder (PTSD). As an exploratory pilot analysis, we also investigated whether this effect depends on the nature of the event (sexual vs. nonsexual trauma).
Methods: Thirty-three patients of both sexes with PTSD were recruited and randomized 1:1 into two groups. One group received oral CBD (300 mg), and the other received a placebo before listening to a digital audio playback of their previously recorded report of the trigger event. Subjective and physiological measurements were taken before and after recall. We analyzed the data in two subsamples: trigger events involving sexual and nonsexual trauma.
Results: In the nonsexual trauma group, the differences between measurements before and after recall were significantly smaller with CBD than placebo; this held true for anxiety and cognitive impairment. However, in the sexual trauma group, the differences were non-significant for both measurements.
Conclusion: A single dose of CBD (300mg) attenuated the increased anxiety and cognitive impairment induced by recalling a traumatic event in patients with PTSD when the event involved nonsexual trauma.

Keywords: Cannabidiol; post-traumatic; sexual trauma; anxiety; cognitive dysfunction

Introduction

Post-traumatic stress disorder (PTSD) is characterized by symptoms that include high levels of anxiety and intrusive memories of the traumatic event; these memories are distressing, recurrent, and involuntary. The condition is associated with symptoms of dissociation, flashbacks, and hypervigilance that are present for at least 30 days.[1] PTSD also involves cognitive abnormalities in processing emotional information.[2] The traumatic experience associated with PTSD must be related to exposure to a concrete episode, such as a death threat, serious injury, or sexual violation.[1]

Three types of medication – selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and atypical antipsychotics – have been used to treat patients with PTSD, with limited results.[3] Several studies have sought to assess the effect of different drugs on the subjective and physiological responses to recalling traumatic situations under controlled experimental conditions. A review of these studies suggests that some pharmacological interventions can alter responses to traumatic memories. The most studied drug is propranolol, but the diversity of experimental protocols and the small number of publications makes it challenging to reach solid conclusions.[4] Therefore, new pharmacological therapeutic alternatives are needed.[3]

It seems reasonable to study cannabidiol (CBD) in this context. This component of the *Cannabis sativa* plant does not produce the typical effects induced by the consumption of the plant[5] and has exhibited numerous therapeutic possibilities, including antiepileptic,[6] antipsychotic,[7] and anxiolytic applications.[8] The anxiolytic effect of CBD, established by consistent results in animals, has also been demonstrated in humans under controlled experimental situations, using a single dose in healthy volunteers and patients with a social anxiety disorder.[8] In this situation, CBD produces an inverted U-shaped dose-response curve, with significant anxiolytic results occurring at 300 mg.[9,10] The anxiolytic action of CBD has

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also been observed in continuous administration over 4 weeks among frontline health care workers.[11,12]

Several studies have associated trauma type with the development and severity of PTSD. Sexual trauma is strongly associated with a diagnosis of PTSD,[13,14] and these patients have a more symptoms than patients with other trigger types; these could be important factors in the therapeutic response to medication.[15-18]

This leads us to hypothesize that CBD could attenuate the subjective manifestations induced by recalling the trigger event in patients with PTSD. This effect could differ depending on the type of traumatic event that caused the disorder.[15]

This study assessed whether administering CBD to patients with PTSD before recalling the traumatic event can attenuate the subjective and physiological manifestations of anxiety induced by this recall. Considering that patients with PTSD due to sexual abuse are an important subgroup in terms of symptomatology,[15] we also investigated, as an exploratory pilot analysis, whether the effects of CBD depend on the nature of the traumatic event.

Methods

Study design and participants

This study was a randomized, parallel-group, double-blind, placebo-controlled trial in patients diagnosed with PTSD. We estimated the sample size based on previous studies that used anxiety-eliciting stimuli to calculate the difference between mean Visual Analog Mood Scale (VAMS) scores in patients who received CBD vs. placebo.[9,19] We estimated a sample size that would yield a significance level of 0.05 and a statistical power of 0.8.[20] Thirty-three participants of both sexes were recruited and randomized by minimization 1:1 into two groups: the CBD group (n=17) and the placebo group (n=16). The groups were matched by sex, age, body mass index (BMI), and symptom severity by a researcher not involved in data collection and analysis.

To identify patients for recruitment, we analyzed the medical records of a large hospital and conducted an active search in outpatient clinics and social media. The inclusion criteria were age between 18 and 60 years and a diagnosis of PTSD according to the DSM-V. The exclusion criteria were: abuse or dependence on psychoactive drugs; the presence of other psychiatric disorders, except for depression and anxiety disorders; and the presence of organic brain syndromes.

Psychological measures

The Portuguese version of the VAMS[19,21,22] was used to analyze subjective manifestations of PTSD. This scale includes four factors: 1) anxiety (items: calm – agitated; tense – relaxed; worried – tranquil); 2) sedation (items: alert – sleepy; attentive – distracted); 3) cognitive impairment (items: difficult reasoning – perceptive; incapable – capable; agile – clumsy; confused – clear ideas; withdrawn – sociable; strong – weak; apathetic – dynamic) and; 4) discomfort (items: satisfied – dissatisfied; happy – sad; hostile – friendly; interested – disinterested).[23]

The SCID-V for the DSM-V was used to diagnose PTSD.[24,25] The severity of PTSD symptoms was assessed using the Posttraumatic Stress Disorder Checklist (PCL-5).[26,27]

Physiological measures

Systolic and diastolic blood pressure (BP), heart rate (HR), and salivary cortisol concentrations were measured before and after traumatic event recall. The Salivette® device (Sarsted, Germany) was used to collect saliva samples. These devices consist of a tube containing a cylindrical cotton pad. The pad was chewed for at least 1 minute and then centrifuged in the tube. The results were determined with enzyme-linked immunosorbent assay (ELISA).

Trauma recall

Adapted from Pitman,[28] the behavioral test for assessing subjective and physiological responses to recall of a traumatic event under controlled experimental conditions involved no editing of the recordings and did not include the neutral procedure. In the first experimental session, a digital audio recording was made of the patients as they described the traumatic event for 90 seconds. After recording, the participants were asked to imagine themselves in the traumatic situation, in the most vivid way possible, for 30 seconds. In the second experimental session, patients listened to their audio recording and then were asked to again imagine the trauma for 30 seconds. All participants received instructions prior to beginning the procedure and were advised that the recordings would be erased upon completion of the experiment.

Medication

CBD was supplied as a powder with 99.6% purity and no other cannabinoids (BioSynthesis Pharma Group; BSPG-Pharm, United Kingdom). The powder was then dissolved in corn oil and packed in gelatin capsules. Each capsule contained a 300 mg dose. The placebo consisted of corn oil packaged in identical capsules.

Procedure

The experimental protocol consisted of two sessions with a 1-week interval between them. In the first session, the informed consent form was signed, the measurements for matching the groups (sex, age, BMI, and PCL-5 score) were performed, and the participants recorded the traumatic event. In the second session, after adapting to the experimental setting (15 minutes), the patients were given CBD or placebo. Ninety minutes later, they underwent the recall procedure. The subjective and physiological measurements (BP, HR, CS, VAMS) were taken before and after the recall event. The study was

conducted at the Laboratório de Psicofarmacologia, Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo em Ribeirão Preto. Table 1 summarizes the experimental protocol.

Data analysis

Clinical and demographic data were analyzed, using the *t*-test for continuous data and Fisher's exact test for nominal data. The remaining data were analyzed using three-way repeated measures analysis of variance (ANOVA). The factors were group (CBD x placebo), trauma (sexual x nonsexual), and phase (before and after the recall event). A significant difference in the phase-group-trauma interaction or phase-trauma interaction prompted an exploratory pilot analysis comparing the effects of CBD in two sub-samples, with and without sexual trauma. For this analysis, the differences (delta) between measurements performed before and after the recall in the CBD and placebo groups were compared using the *t*-test in each sub-sample. For all statistics, a p-value < 0.05 was considered statistically significant. SPSS version 26.0 was used for all statistical analyses.

Ethics statement

This study was approved by the research ethics committee of the Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP) (CAAE number: 2.405.299). Before enrollment in the study arms, informed consent was obtained from all participants.

Results

Table 2 shows the demographic characteristics of the study participants.

Patient sex, age, BMI, and PCL-5 score did not differ significantly between the placebo and CBD groups.

Psychological measures

Table 3 shows the results of three-way repeated measures ANOVA for the VAMS subsets before and after the recall challenge.

Significantly higher VAMS scores were observed for all factors after the patients recalled the traumatic event (phase). There was also a significant phase-group interaction in cognitive impairment factor, with a greater increase in scores after recall in the placebo group (10.50) than in the CBD group (3.75). The phase-group-trauma interaction was significant for the discomfort factor, and there was a trend towards significance in anxiety. Moreover, there was a significant phase-trauma interaction in the sedation factor.

Since there was a significant interaction between phase-group-trauma, we performed an exploratory analysis by dividing the sample into two sub-samples (sexual and nonsexual trauma). The PTSD-triggering event was sexual abuse in 14 patients and nonsexual trauma in 19. The nonsexual types of traumatic events included being threatened with firearms (nine patients), physical violence (four patients), indirect trauma (four patients), and accidents (two patients). In the sexual trauma

Table 1 Phases and procedures of the experimental session

Phase	Procedure
Day 0	
Recruiting	Participants recruiting via social media or hospital outpatient. SCID-5 interview application and assessment of eligibility.
Day 1	
Pairing	Calculation of BMI and application of PCL-5
Behavioral trial (HCRP)	Recording the trauma report (90 seconds) Imagine the traumatic event (30 seconds)
Day 2	Habituation (15 minutes)
Drug administration and behavioral trial (HCRP)	CBD or PLC (90 minutes) BP, HR and SC, VAMS. Listening to the trauma report (90 seconds) Imagining the traumatic event (30 seconds) BP, HR and SC, VAMS.

BMI = body mass index; BP = blood pressure; CBD = cannabidiol; HCRP = Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; HR = heart frequency; PCL-5 = Posttraumatic Stress Disorder Checklist; PLC = placebo; SC = salivary cortisol; VAMS = Visual Analog Mood Scale.

Table 2 Sociodemographic and clinical characteristics of the groups

Variable	CBD	PLC	Statistics
Group size (n – male/female)	17 – 4/13	16 – 4/12	$X^2 = 0.010$; p = 0.922
Age	33.94 (11.55)	32.50 (13.01)	t = 0.337; p = 0.738
BMI	25.69 (5.06)	28.03 (6.57)	t = -1.14; p = 0.26
PCL-5	52.47 (12.08)	54.12 (9.21)	t = -0.44; p = 0.663

Data presented as mean (standard deviation), unless otherwise specified.
BMI = body mass index; CBD = cannabidiol; PCL-5 = Posttraumatic Stress Disorder Checklist; PLC = placebo.

Table 3 VAMS factor scores before and after behavioral tests and the three-way repeated measures ANOVA results

VAMS factor/phase	Cannabidiol (n=17) (mean [SD])	Placebo (n=16) (mean [SD])	Interaction			
			Phase	Phase x group	Phase x trauma	Phase x group x trauma
Anxiety			$F_{1,29} = 73.7$ ($p < 0.001$)* $\eta_p^2 = 0.72$	$F_{1,29} = 0.38$ ($p = 0.54$) $\eta_p^2 = 0.01$	$F_{1,29} = 1.03$ ($p = 0.32$) $\eta_p^2 = 0.03$	$F_{1,29} = 3.60$ ($p = 0.07$)* $\eta_p^2 = 0.11$
Before	40.34 (14.55)	36.77 (14.92)				
After	54.94 (15.05)	55.00 (12.57)				
Sedation			$F_{1,29} = 28.6$ ($p < 0.001$)* $\eta_p^2 = 0.50$	$F_{1,29} = 0.69$ ($p = 0.41$) $\eta_p^2 = 0.02$	$F_{1,29} = 3.22$ ($p = 0.08$)** $\eta_p^2 = 0.10$	$F_{1,29} = 0.29$ ($p = 0.60$) $\eta_p^2 = 0.01$
Before	58.52 (10.40)	54.34 (14.53)				
After	42.23 (14.82)	42.03 (13.55)				
Cognitive impairment			$F_{1,29} = 23.4$ ($p < 0.001$)* $\eta_p^2 = 0.45$	$F_{1,29} = 4.28$ ($p = 0.048$)** $\eta_p^2 = 0.13$	$F_{1,29} = 0.03$ ($p = 0.86$) $\eta_p^2 = 0.001$	$F_{1,29} = 0.61$ ($p = 0.44$) $\eta_p^2 = 0.02$
Before	45.40 (11.69)	43.36 (11.95)				
After	49.15 (13.01)	53.41 (15.78)				
Discomfort			$F_{1,29} = 29.8$ ($p < 0.001$)* $\eta_p^2 = 0.51$	$F_{1,29} = 0.14$ ($p = 0.72$) $\eta_p^2 = 0.005$	$F_{1,29} = 0.12$ ($p = 0.72$) $\eta_p^2 = 0.004$	$F_{1,29} = 4.48$ ($p = 0.043$)* $\eta_p^2 = 0.13$
Before	37.71 (11.8)	40.86 (11.81)				
After	46.90 (12.21)	49.84 (11.16)				

ANOVA = analysis of variance; VAMS = Visual Analog Mood Scale.
* $p < 0,05$; ** $p > 0.05$ and < 0.1.

subsample, seven participants received CBD and seven received placebo; in the nonsexual trauma subsample, 10 participants received CBD and nine received placebo. Table 4 shows the demographic characteristics of the groups in the two sub-samples.

Patient sex, age, BMI, PCL-5 score, marital status, time since the trauma, education level, occupation, medication use, and comorbidities did not significantly differ between the placebo and CBD recipients in either subsample. However, there were sex differences between the sexual and nonsexual trauma subsamples in the CBD group (Fisher's exact test = 6.5; p = 0.035). Moreover, patients with sexual trauma were younger and had a shorter time since the traumatic event than those with nonsexual trauma.

The differences between VAMS factor measurements before and after the recall event are shown in Figure 1.

Among those with nonsexual trauma, the change in VAMS anxiety before and after the recall event was significantly lower in the CBD group than the placebo group (mean difference = -9.82; p = 0.033; 95% confidence interval [95%CI] -18.74 to -0.91). The difference between the CBD and placebo subgroups was not significant among those with sexual trauma (mean difference = 5.00; p = 0.497; 95%CI -10.56 to 20.57). CBD led to significantly greater reductions in VAMS anxiety for nonsexual than sexual trauma (mean difference = 11.40; p = 0.035; 95%CI 0.90-21.89).

Regarding VAMS cognitive impairment before and after the recall event, those with nonsexual trauma had a significantly greater reduction in the CBD group than the placebo group (mean difference = -8.21; p = 0.008; 95% CI -13.94 to -2.47). This difference was not observed among those with sexual trauma (mean difference = -3.70; p = 0.524; 95%CI -16.00 to 8.60).

Regarding VAMS sedation, there was no significant difference in scores before and after the recall event among those with nonsexual (mean difference = -1.67; p = 0.713; 95%CI -11.10 to 7.75) or sexual trauma (mean difference = -7.72; p = 0.525; 95%CI -33.39 to 17.95). Similarly, there was no significant difference in VAMS discomfort among those with nonsexual (mean difference = -5.81; p = 0.202; 95%CI -15.03 to 3.42) or sexual trauma (mean difference = 8.28; p = 0.123; 95%CI -2.61 to 19.17).

Physiological measures

Table 4 shows the values and the three-way repeated measures ANOVA results for physiological measures taken before and after the recall event.

Both systolic BP and HR were significantly higher after recalling the traumatic event (phase). A phase-trauma interaction was observed in the HR results.

The delta scores of physiological variables before and after recall did not differ significantly in either trauma subsample in either group. In the sexual trauma subsample, the mean difference in salivary cortisol was 0.07 (p = 0.102; 95%CI -0.02 to 0.16), whereas it was 0.02 (p = 0.814; 95%CI -0.15 to 0.19) among those with nonsexual trauma. Among those with sexual trauma, the mean difference in systolic BP was -1.29 (p = 0.879; 95%CI -19.24 to 16.67), while among those with nonsexual trauma it was -4.27 (p = 0.398; 95%CI -14.68 to 6.13). Among those with sexual trauma, the mean difference in diastolic BP was -4.14 (p = 0.470; 95%CI -16.25 to 7.96), while among those with nonsexual trauma it was -3.22 (p = 0.397; 95%CI -11.05 to 4.60). Among those with sexual trauma, the mean difference in HR was 2.43 (p = 0.521; 95%CI -5.57 to 10.43), while among those with nonsexual trauma it was -0.07 (p = 0.974; 95% CI -4.25 to 4.11).

Discussion

We observed that patients with PTSD, when asked to recall their triggering event, experience significantly higher subjective anxiety, alertness, discomfort, and cognitive impairment. They also experience a significantly higher physiological response, e.g., systolic BP and HR. This demonstrates the adequacy of testing the effects of drugs on subjective and physiological parameters influenced by trauma recall.

The subjective effects of recalling a traumatic event on cognitive impairment were significantly lower in the CBD group than the placebo group. This could indicate that CBD interferes with aversive memory reconsolidation, as has been observed in preclinical studies.[29] However, we did not test this hypothesis in our experiment.

The increase in subjective cognitive impairment after recalling a traumatic event may be associated with the cognitive interference of the event itself.[30] The results of a previous study may support the lower cognitive impairment we observed in the CBD group: in healthy volunteers, CBD significantly increased VAMS "clear-headed" (opposite of "fuzzy") and "quick-witted" (opposite of "mentally slow") scores in healthy volunteers.[5]

Our post-hoc pilot analysis showed that CBD's impact on the subjective effects of recalling a traumatic event depends on whether the trauma that triggered PTSD was of a sexual nature. In patients with nonsexual trauma, CBD significantly attenuated anxiety and cognitive impairment after recall. Regarding anxiety, our result is consistent with previous observations of this cannabinoid's anxiolytic effects in preclinical studies, healthy volunteers, frontline healthcare workers, and patients with social anxiety disorders.[8,11,12] Regarding cognitive impairment, our results are consistent with findings across the sample and discussed above. Unlike the phase-group interaction for anxiety and cognitive impairment, the physiological variables were not significantly attenuated in the trauma subsamples. This dissociation between subjective mood and physiological effects following acute administration of CBD is consistent with findings in healthy volunteers[10,20] and patients with social phobia.[31]

The fact that CBD had no significant effect on the subjective effects of recalling a traumatic event in patients with sexual trauma could be related to the greater symptom severity associated with such trauma.[15-18] Of the three commonly reported PTSD trauma types (sexual trauma, nonsexual physical violence, and the unexpected

Table 4 Sociodemographic and clinics characteristics of the samples and groups

	Comparison between samples			Comparison between groups					
	Trauma			Sexual trauma (n=14)			Other trauma (n=19)		
Variable	Sexual	Other	p-value	CBD	PLC	p-value	CBD	PLC	p-value
Group size (n – male/female)	14 (1/13)	19 (7/12)	0.10	7 (0/7)	7 (1/6)	1.00	10 (4/6)	9 (3/6)	1.00
Age (mean [SD])	25.15 (6.00)	39.21 (12.10)	< 0.001*	23.57 (3.87)	26.71 (7.50)	0.34	41.2 (9.22)	27.9 (14.90)	0.47
BMI (mean [SD])	25.18 (7.24)	28.04 (4.45)	0.17	22.52 (4.54)	27.84 (8.75)	0.18	27.9 (4.31)	28.18 (4.86)	0.90
PCL-5	54.29 (11.50)	52.53 (10.25)	0.65	52.57 (13.63)	56.00 (9.68)	0.60	52.40 (11.65)	52.67 (9.14)	0.96
Marital status									
Single	5 (35.70)	6 (31.60)	1.00	3 (42.90)	2 (28.60)	1.00	2 (20.00)	4 (44.40)	0.35
Cohabiting	9 (64.30)	13 (68.40)		4 (57.10)	5 (71.40)		8 (80.00)	5 (55.60)	
Time since the trauma, years									
< 10	6 (42.90)	16 (84.20)	0.02†	4 (57.10)	2 (28.60)	0.59	8 (80.00)	8 (88.90)	1.00
⩾ 10	8 (57.10)	3 (15.80)		3 (42.90)	5 (71.40)		2 (20.00)	1 (11.10)	
Education, years									
< 11	4 (28.60)	9 (47.40)	0.31	1 (14.30)	3 (42.90)	0.56	6 (60.00)	3 (33.30)	0.37
⩾ 11	10 (71.40)	10 (52.60)		6 (85.70)	4 (57.10)		4 (40.00)	6 (66.70)	
Employment									
Active	5 (35.70)	7 (36.80)	1.00	3 (42.90)	2 (28.60)	1.00	2 (20.00)	5 (55.60)	0.17
Inactive	9 (64.30)	12 (63.20)		4 (57.10)	5 (71.40)		8 (80.00)	4 (44.40)	
Medication use									
Yes	7 (50.00)	9 (47.40)	1.00	4 (57.10)	3 (42.90)	1.00	5 (50.00)	4 (44.40)	1.00
No	7 (50.0)	10 (52.60)		3 (42.90)	4 (57.10)		5 (50.00)	5 (55.60)	
Comorbidities									
Yes	10 (71.40)	12 (63.20)	0.72	7 (100.0)	3 (42.90)	0.07**	8 (80.00)	4 (44.40)	0.17
No	4 (28.60)	7 (36.80)		0 (0.0)	4 (57.10)		2 (20.00)	5 (71.40)	

Data presented as n (%), unless otherwise specified.
BMI = body mass index; CBD = cannabidiol; PCL-5 = Posttraumatic Stress Disorder Checklist; PLC = placebo; SD = standard deviation.
* $p < 0.05$; ** $p > 0.05$ and < 0.1.

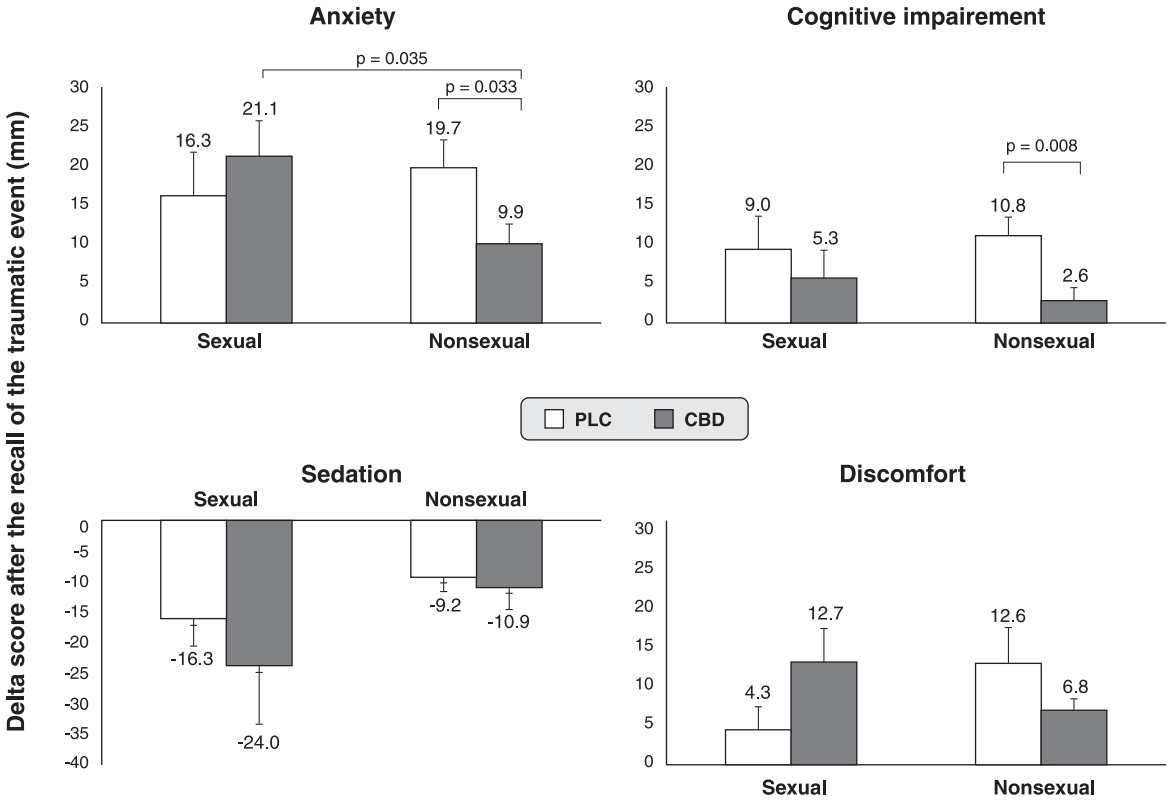

Figure 1 Visual Analog Mood Scale delta scores after recalling the traumatic event in post-traumatic stress disorder patients with sexual and nonsexual traumas. In the nonsexual sample, the cannabidiol (CBD) group (n=10) had significantly lower anxiety and cognitive impairment than the placebo group (n=9). However, no significant differences were observed between CBD (n=7) and placebo (n=7) in the sexual sample.

death of a loved one), sexual trauma is associated with a higher overall symptom score and longer symptom duration.[15] Patients with sexual trauma-related PTSD may need a higher dose of CBD than that used in this study. We chose a 300-mg dose based on studies in healthy volunteers.[9,10] However, studies in patients with social anxiety disorder show that anxiolytic effects are not observed until the dose reaches 600 mg.[31] In line with this observation, a case report on a patient with sexual trauma reported that, although a single dose of CBD (300 mg) did not attenuate trauma recall-induced anxiety, improvement was noted after 1 week of daily administration.[32] The finding that the response to CBD depends on the type of trauma that induced PTSD indicates the heterogeneity of this disorder.[15]

One limitation of the present study is that the mean patient age and time since the traumatic event were significantly lower among those with sexual trauma than nonsexual trauma, which could have influenced the non-attenuation of anxiety in the sexual trauma subsample. However, the regression analyses of a cross-sectional study showed that PTSD symptoms are not associated with patient age at the initial trauma.[16] The sex difference between the subsamples in the CBD group, i.e., the predominance of women in the sexual trauma subgroup, is to be expected according to epidemiological data.[33] In an exploratory analysis (data not shown), we found that patient sex had no influence on the effects of CBD. Another limitation is that the analysis was not corrected for multiple comparisons. However, the study's primary measure was the VAMS, and, to the best of our knowledge, this correction has not been used in the literature to analyze this scale's four factors. Finally, the small number of participants is another limitation and reflects the difficulty of recruiting patients with PTSD who are willing to recall their traumatic experiences.

In conclusion, this study shows that a single 300-mg dose of CBD attenuates the cognitive impairment induced by recalling the triggering event in patients with PTSD. A post-hoc experimental pilot analysis suggested that CBD's impact on the subjective effects of recalling the event depend on the type of trauma that triggered PTSD. In nonsexual trauma, CBD attenuated the increased anxiety and cognitive impairment of recall. However, it failed to do so when the event was sexual in nature. More extensive double-blind chronic placebo-controlled clinical trials using higher doses of CBD are needed to confirm and expand the potential role of CBD in treating patients with PTSD.

Table 5 Physiological measures and three-way repeated measures ANOVA results

Physiological measures/phase	Cannabidiol (n=17) (mean [SD])	Placebo (n=16) (mean [SD])	Interaction			
			Phase	Phase x group	Phase x trauma	Phase x group x trauma
Systolic blood pressure			$F_{1,29} = 8.20$ ($p = 0.008$)* $\eta_p^2 = 0.22$	$F_{1,29} = 0.38$ ($p = 0.54$) $\eta_p^2 = 0.13$	$F_{1,29} = 0.67$ ($p = 0.42$) $\eta_p^2 = 0.02$	$F_{1,29} = 0.11$ ($p = 0.74$) $\eta_p^2 = 0.004$
Before	119.88 (13.57)	119.12 (14.12)				
After	124.52 (15.65)	126.87 (21.30)				
Diastolic blood pressure			$F_{1,29} = 2.00$ ($p = 0.17$) $\eta_p^2 = 0.07$	$F_{1,29} = 1.32$ ($p = 0.26$) $\eta_p^2 = 0.04$	$F_{1,29} = 0.17$ ($p = 0.68$) $\eta_p^2 = 0.006$	$F_{1,29} = 0.02$ ($p = 0.89$) $\eta_p^2 = 0.001$
Before	77.71 (10.31)	76.44 (11.31)				
After	78.06 (9.18)	80.44 (13.07)				
Heart rate			$F_{1,29} = 4.84$ ($p = 0.04$)* $\eta_p^2 = 0.14$	$F_{1,29} = 0.37$ ($p = 0.55$) $\eta_p^2 = 0.01$	$F_{1,29} = 6.64$ ($p = 0.015$)* $\eta_p^2 = 0.19$	$F_{1,29} = 0.41$ ($p = 0.53$) $\eta_p^2 = 0.01$
Before	79.88 (10.36)	81.62 (10.09)				
After	82.05 (11.18)	82.93 (11.18)				
Salivary cortisol			$F_{1,29} = 0.39$ ($p = 0.54$) $\eta_p^2 = 0.01$	$F_{1,29} = 0.79$ ($p = 0.38$) $\eta_p^2 = 0.03$	$F_{1,29} = 0.03$ ($p = 0.86$) $\eta_p^2 = 0.001$	$F_{1,29} = 0.24$ ($p = 0.63$) $\eta_p^2 = 0.01$
Before	0.19 (0.25)	0.17 (0.17)				
After	0.20 (0.18)	0.14 (0.12)				

ANOVA = analysis of variance; SD = standard deviation.
* $p < 0.05$.

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Disclosure

JASC was a consultant and/or has received speaker fees and/or sits on the advisory board and/or receives research funding from Janssen-Cilag, Torrent Pharm, Prati-Donaduzzi, PurMed Global, and BSPG Pharm over the past 3 years. JASC, JECH, and AWZ are coinventors of the patent ''Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023,'' Def. US number Reg. 62193296; July 29, 2015; INPI on August 19, 2015 (BR1120150164927; Mechoulam R, Zuardi AW, Kapczinski F, Hallak JEC, Guimarães FS, Crippa JAS, Breuer A). Universidade de São Paulo (USP) has licensed this patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1) and has an agreement with Prati-Donaduzzi to ''develop a pharmaceutical product containing synthetic CBD and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders.'' JASC, JECH, and AWZ are coinventors of the patent ''Cannabinoid-containing oral pharmaceutical composition, method for preparing and using same,'' INPI on September 16, 2016 (BR 112018005423-2). The other authors report no conflicts of interest.

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