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Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial

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ABSTRACT

Background and Aims Cocaine use disorder (CUD) is a significant public health concern for which no efficacious pharmacological interventions are available. Cannabidiol (CBD) has attracted considerable interest as a promising treatment for addiction. This study tested CBD efficacy for reducing craving and preventing relapse in people with CUD. **Design** Single-site double-blind randomized controlled superiority trial comparing CBD with placebo. **Setting and Participants** Centre Hospitalier de l'Université de Montréal, Canada. Seventy-eight adults (14 women) with moderate to severe CUD participated. **Intervention** Participants were randomly assigned (1 : 1) by stratified blocks to daily 800 mg CBD (n = 40) or placebo (n = 38). They first underwent an inpatient detoxification phase lasting 10 days. Those who completed this phase entered a 12-week outpatient follow-up. **Measurements** Primary outcomes were drug–cue-induced craving during detoxication and time-to-cocaine relapse during subsequent outpatient treatment. **Findings** During drug–cue exposure, craving scores [mean ± standard deviation (SD)] increased from baseline by 4.69 (2.89) versus 3.21 (2.78) points, respectively, in CBD (n = 36) and placebo (n = 28) participants [confidence interval (CI) = −0.33 to 3.04; P = 0.069; Bayes factor = 0.498]. All but three participants relapsed to cocaine by week 12 with similar risk for CBD (n = 34) and placebo (n = 27) participants (hazard ratio = 1.20, CI = 0.65–2.20, P = 0.51; Bayes factor = 0.152). CBD treatment was well tolerated and associated mainly with diarrhoea. **Conclusions** CBD did not reduce cocaine craving or relapse among people being treated for CUD.

Keywords Addiction, cannabidiol, cocaine, craving, human, relapse.

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INTRODUCTION

More than 18 million people world-wide use cocaine [1], and 16% of them will develop a cocaine use disorder (CUD) [2]. Given its association with high rates of health and social problems [3], together with premature mortality [4], CUD has become a public health issue. An important factor predicting relapse is the intense desire (craving) to use cocaine [5]. CUD and related craving are mainly managed with psychosocial interventions such as cognitive behavioural therapy and contingency management. These strategies alone are often insufficient to induce behavioural changes or a reduction in cocaine use and relapse [6]. Several systematic reviews on CUD pharmacological treatments found weak efficacy evidence to improve cocaine craving and time to relapse [7,8]. Consequently, there is an urgent need to identify novel treatments to help individuals with CUD.

Pre-clinical findings suggesting that cannabinoids may decrease drug use [9,10] have motivated an enthusiastic call for research into cannabidiol (CBD) as a promising intervention for CUD [11–13]. CBD has a favourable tolerability profile [14] together with numerous physiological and neuroprotective properties. For example, it protects

against cocaine-induced seizures and hepatotoxicity in animals [15]. Moreover, CBD possesses anxiolytic properties in clinical populations and can decrease autonomic arousal [16]. This is important, as stress is a potent cocaine-craving inducer [17] and a potential target for new addiction interventions. The exact mechanism by which CBD impacts cocaine use is still unknown, but several have been hypothesized (e.g. hippocampal neurogenesis [18], reviewed here [12]).

Animal and human studies also reported CBD as a potential treatment for addictive disorders. Hence, sustained administration of CBD in rodents inhibits cocaine self-administration and context- and stress-induced reinstatement of cocaine-seeking behaviour [12,19]. Pre-clinical studies also demonstrated that CBD inhibits cue-induced heroin-seeking behaviours for up to 2 weeks following the last administration [20], while a small randomized clinical trial (RCT) showed that CBD decreases cue-induced craving and anxiety in individuals with heroin use disorder (HUD) [21]. Also, a recent RCT revealed that CBD was efficacious in reducing cannabis use in individuals with cannabis use disorder [22]. Finally, a cross-over RCT showed that CBD decreased attention bias of cigarette cues compared with placebo [23]. However, short-term treatment with 300 mg CBD was not effective in reducing craving in individuals with CUD [24].

However, it remains unclear whether individuals with CUD can benefit from a high dose of CBD in order to decrease their cocaine craving and, ultimately, the risk of relapse. In this RCT, we primarily aimed to test CBD efficacy in reducing drug–cue-induced craving and increasing time-to-cocaine relapse in recently abstinent individuals with CUD. Furthermore, we secondarily aimed to assess CBD efficacy in reducing stress-induced craving and cocaine use. We hypothesized that CBD would be superior to placebo in reducing drug–cue and stress-induced cravings, increasing time-to-cocaine relapse and decreasing cocaine use.

METHODS

Study design

This Phase II double-blind, randomized, parallel-group, placebo-controlled superiority trial was conducted at the Centre hospitalier de l'Université de Montréal (CHUM), Quebec, Canada, and followed the Tri-Council Policy Statement, the Helsinki declaration, the Good Clinical Practice (International Conference on Harmonization Guidelines), the Good Manufacturing Practices and Health Canada division 5 guidelines. The CHUM's ethics committee approved the study and all participants signed an informed consent. The trial was divided into two phases: a 10-day inpatient detoxification (Phase I) followed by a 12-week outpatient follow-up (Phase II). Only participants who remained inpatient for all 10 days were eligible for Phase II. Participants were compensated up to $400.

Participants

Recruitment occurred between 20 July 2016 and 25 June 2019. We included adults aged between 18 and 65 years diagnosed with current CUD [Structured Clinical Interview (SCID) for the DSM-V] [25] and who had consumed cocaine within 2 weeks prior to admission [time-line follow-back (TLFB)] [26]. Only participants speaking English or French and able to consent were eligible. We excluded participants with severe and/or unstable medical or psychiatric condition [Mini International Neuropsychiatric Interview (MINI) version 7.0] [27], immunodeficiency, hypersensitivity to cannabinoids or under treatment with medications interacting with CBD. Participants diagnosed with another substance use disorder (except nicotine) that would require treatment were ineligible. Men with history of fertility problems, pregnant or breastfeeding women and individuals planning to conceive within the year were excluded. Women of childbearing age needed to agree to use a medically acceptable form of contraception.

Participants were recruited within the CHUM's research centre, in clinical programs and from newspapers, on-line advertising and word of mouth. Potential participants were pre-screened and invited for an in-person screening visit. The study was explained, and an informed consent form was signed before full-eligibility assessment, which included a socio-demographic questionnaire, a urine drug screening and blood work, two standardized evaluation tools (MINI, SCID), an electrocardiogram and an addiction physician evaluation.

Randomization and masking

Participants were assigned to one of two trial arms (placebo or CBD, 1 : 1 ratio) using stratified blocked randomization. The stratification variables were sex [28] and baseline severity of cocaine dependence group ($<$ versus $\geq$ 10) assessed by the Severity of Dependence Scale (SDS) [29]. An independent biostatistician created the computer-generated randomization sequence. Placebo and CBD solutions looked and tasted exactly alike. Participants and research staff were blinded to treatment allocation. The pharmacy staff kept each participant's treatment assignment in separate envelopes to avoid unblinding of all participants in case of emergency. The James blinding index was used to evaluate treatment blinding [30].

Procedures

Treatment arms

Participants received either synthetic CBD (300 mg/ml) or placebo oral solution (clear, colourless to pale yellow-brown; Insys Therapeutics, Chandler, AZ, USA) for 92 days. These solutions contained vitamin E, saccharin, strawberry flavour and medium chain triglycerides. For Phase I, oral solution was administered daily at 10.00 a.m. On days 2 and 3, we gave 400 mg (1.3 ml) of either CBD or placebo to participants and then increased the dose to 800 mg/day (2.7 ml) for the rest of the study. Subjects (CBD, $n = 1$) who reported intolerable side effects with the 800-mg dose were administered 400 mg for the remainder of the trial. For Phase II, we provided bottles weekly to participants who were instructed to take 800 mg/day (2.7 ml) in the morning. Dosage selection was based on safety and clinical data [31].

Standard treatment and follow-up

During Phase I (days 1–10), participants were admitted on the CHUM addiction inpatient unit without possibility to access substances. In addition to receiving standard medical care, participants attended psycho-education group therapy sessions. Blood pressure and heart rate were monitored three times daily. In the event of significant insomnia, participants received diphenhydramine and/or trazodone, but not 24 h before the experimental craving session.

During Phase II (weeks 1–12), participants attended weekly visits during which they received the bottled medication. Every week, participants could attend a relapse prevention group session. Standard medical follow-up was conducted every 4 weeks to ensure participants' safety. Biological sampling (urine and blood) and subjective report measures were collected during weekly study visits (Supporting information, Table S1 provides the study timeline and assessment schedule).

Cue-induced craving experimental session (Phase I)

On day 6, the research staff gathered participants' information to develop three 5-min personalized script-driven guided imagery scenarios [32]: (1) a neutral relaxing event (e.g. day at the beach), (2) a cocaine-use-related event (e.g. party with friends) and (3) a stressful situation (e.g. conflict with a friend). Each scenario was drafted and audiotaped. On day 8, participants underwent the cue-induced experimental session. The scenario order was counterbalanced and randomized across subjects.

Outcomes

The primary outcomes were drug–cue-induced craving (Phase I) and time-to-cocaine relapse (Phase II). We calculated self-reported drug–cue-induced craving as the difference in craving scores [visual analogue scale (VAS) ranging from 0 to 10] between after and before the drug–cue-induced imagery session on day 8. We assessed time-to-cocaine relapse over 12 weeks by counting the days between the detoxification discharge and the first day of cocaine use. This outcome was determined subjectively (TLFB) and objectively by weekly urinalysis. Urine samples were analyzed by rapid chromatographic immunoassay for benzoylecgonine (major cocaine metabolite) quantification with a lower limit of 150 ng/ml. In the event of missing data, we considered that the participant relapsed. After a relapse, participants were expected to continue weekly follow-up.

Our secondary outcomes included stress-induced craving (Phase I) and cocaine use (Phase II). We calculated self-reported stress-induced craving as the difference in craving scores (using the VAS) between after and before a stress-induced craving session on day 8. We assessed cocaine use by calculating the percentage of positive urine tests out of the 12 urine samples collected during follow-up [33]. All missing urine tests were considered positive.

Our exploratory outcomes included daily cocaine craving, cocaine withdrawal symptoms, self-reported days of cocaine use and sustained abstinence. We measured daily cocaine craving every 2 days during Phase I and every 2 weeks during Phase II using both the VAS for craving and the Cocaine Craving Questionnaire-Brief (CCQ-Brief). Cocaine withdrawal symptoms were evaluated every 2 days during Phase I and monthly during Phase II using the Cocaine Selective Severity Assessment (CSSA). TLFB was used to calculate the percentage of self-reported days of cocaine use during Phase II. Sustained abstinence was defined as 21 consecutive days without cocaine relapse and calculated the proportion of individuals finishing Phase I who reached sustained abstinence at least once during Phase II.

Adverse events (AE) and serious adverse events (SAE) were elicited throughout the trial using the Systematic Assessment for Treatment Emergent Events (SAFTEE) tool [34]. A complete routine blood work was administered to ensure participants' safety at different time-points during the study. For Phase I, study compliance was defined as the proportion of expected daily doses administered. For Phase II, medication compliance was assessed by calculating the volume of taken medication inside the returned bottles and by analyzing blood samples. Blood CBD levels were measured at 9.00 a.m. on day 8 (Phase I), weeks 4 and 12 (Phase II). Only on day 9, blood CBD level was measured at 1.00 p.m. Plasma CBD was determined by liquid/liquid extraction in presence of acetonitrile and internal standard CBD-d3, following by dabsyl-chloride derivatization of CBD. Dabsyl CBD was measured by high-performance liquid chromatography tandem ESI-MS/MS in positive mode [35].

Statistical analyses

This study was registered with ClinicalTrials.gov, NCT02559167. An independent data safety and monitoring board was assembled to ensure human safety and advise on study conduct. Analyses were performed using the SAS version 9.4 software (SAS Institute, Cary, NC, USA). For all analyses, the level of significance was 5% except for the primary analysis where a Bonferroni-corrected value of 2.5% was used to account for the primary outcomes' multiplicity. Demographic and baseline characteristics of randomized participants are reported using descriptive statistics.

Sample size

We calculated sample size using an 80% power and a 2.5% Bonferroni-corrected significance level (two primary hypotheses) and adjusted to a 10% loss to follow-up. For the craving outcome, the sample size calculation was based on Sinha *et al.*'s findings [36] using a two-tailed *t*-test and a 40% minimum clinically important difference for the relative reduction of the mean VAS craving in the CBD group. For the time-to-cocaine relapse outcome, we aimed to detect a 60% hazard reduction [hazard ratio (HR) = 0.4] in the CBD group using the log-rank test. The resulting sample size was 110 (55 per group).

Primary analysis

The drug–cue-induced craving responses obtained on day 8 (Phase I) were analyzed with a multiple linear regression model adjusting the mean difference in post–pre changes in VAS craving scores for the two stratification variables: sex and baseline SDS score. In addition, the pre-imagery VAS score was added as a covariate when the correlations between the pre- and post-imagery craving measures were different between groups (accounting for an eventual regression to the mean). The model-adjusted treatment effect was tested using a two-tailed *t*-test.

Data on cocaine relapse were analyzed using time-to-event methodology. All participants who completed Phase I and started Phase II were included in this analysis (CBD, $n = 34$; placebo, $n = 27$). Lost to follow-up participants without relapse events were considered as having relapsed. Participants who completed the follow-up without relapsing were right censored. A multivariate Cox proportional hazards model assessed the intervention effect on the risk of cocaine relapse. This model adjusted this effect for the stratification variables (sex and baseline SDS score). In the multivariate Cox model, the intervention effect was estimated by the adjusted HR. Its statistical significance was tested using the two-tailed Wald test.

Bayes factors (BF) were computed for each primary analysis. BF values > 3.00 or < 0.33, respectively, favour the experimental or the null hypothesis, whereas in-between values are considered anecdotal evidence [37,38]. Each analysis was complemented by a sensitivity analysis where any baseline characteristic associated (P-value < 0.1) with the primary outcome was added as covariate in the model. In addition, a logistic regression model on cocaine relapse including all randomized participants was performed as complementary analysis.

Secondary analysis

The stress–cue-induced craving responses were analyzed using the same methodology as for the drug–cue-induced craving with a 5% level of significance. For cocaine use, the percentage of visits with a positive urine test was analyzed based on Jones *et al.*'s approach [39]. Positive urine tests were analyzed with an independent *t*-test with a 5% level of significance.

Exploratory analysis

The daily cocaine craving VAS scores from both phases were combined and analyzed using a generalized estimating equation (GEE) model with sex and continuous SDS score as covariates. Considering possible phase variation in the treatment effect, the phase was added as a covariate in the model, together with a treatment–phase interaction. We used the same approach to analyze the CCQ-Brief and CSSA score results. The sustained abstinence and self-reported days of cocaine use were analyzed with independent-group Student's *t*-tests.

RESULTS

Figure 1 illustrates the Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Among the 151 screened individuals, 78 were randomized into the two treatment groups. Due to interruptions in access to oral solutions, the enrolment was terminated at 78 participants. Forty participants received CBD and 38 participants received a placebo. Sixty-two participants (CBD, $n = 35$; placebo, $n = 27$) successfully completed detoxification. A total of 50 participants fully completed the study (CBD, $n = 27$; placebo, $n = 23$), which corresponds to a follow-up rate of 80.6% (CBD, 79.4%; placebo, 82.1%) for Phase II and 63.3% for the entire trial (CBD, 67.5%; placebo, 59.0%).

Table 1 summarizes the baseline and socio-demographic characteristics in each treatment group.

Figure 2 illustrates the changes in craving scores following a cocaine, stress or neutral cue imagery session in both treatment groups during Phase I. Table 2 provides the related data. Following a neutral cue, participants' subjective cravings did not increase, which confirms the validity of our imagery scenarios. Both groups similarly increased their subjective cravings following a cocaine

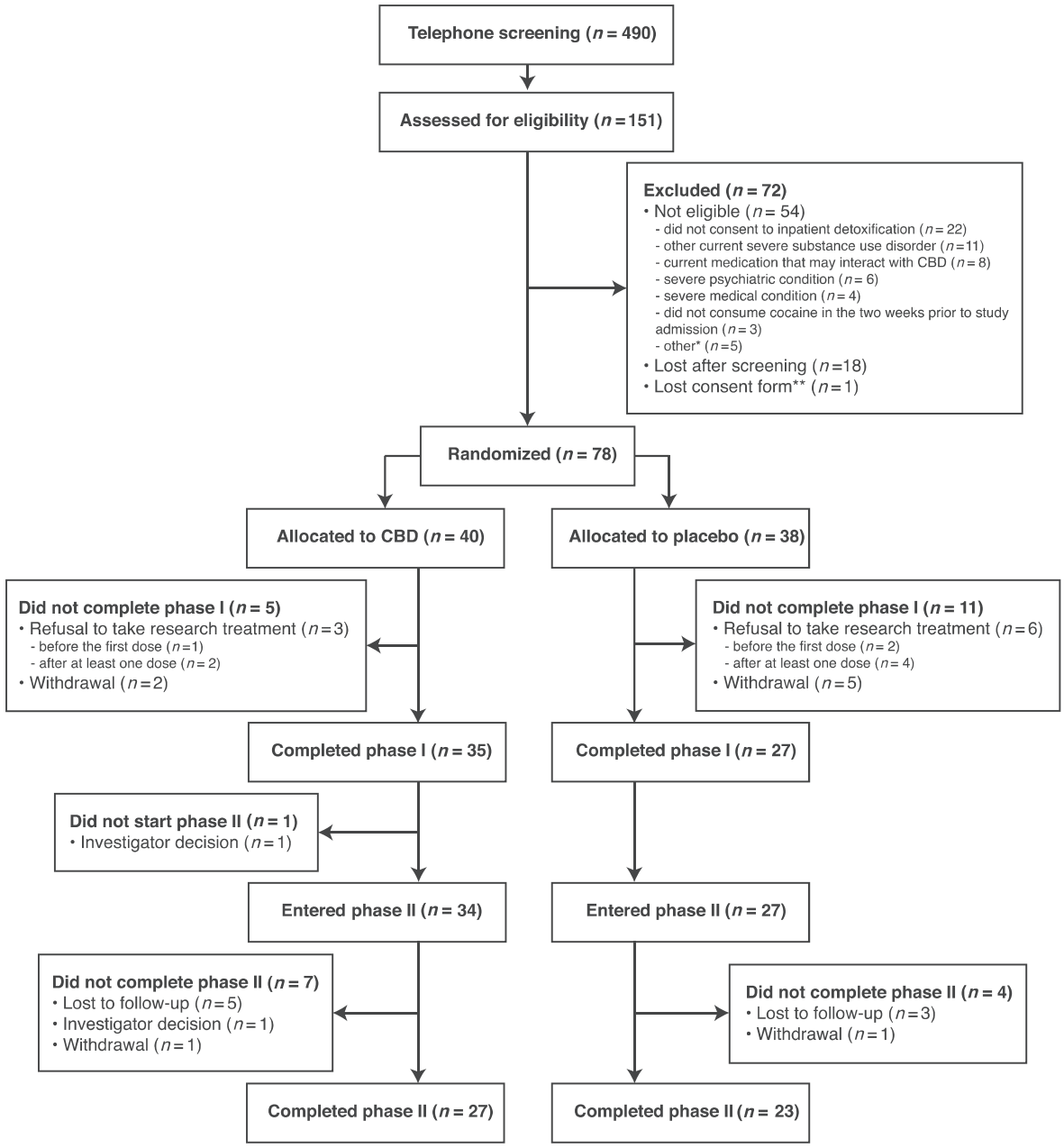


FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow-chart of participants with cocaine use disorder (CUD) involved in this trial. Participants are considered lost to follow-up when they missed two consecutive visits. *Other reasons for ineligibility included men with fertility problems (*n* = 2), immunocompromised participants (*n* = 2) and not currently moderate or severe CUD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria (*n* = 1). **One participant's consent form was lost. When asked, this participant refused to re-consent, which ended her participation. This was reported to the data safety and monitoring board who requested that no data from this participant be used in the study. CBD = cannabidiol; *n* = number of participants

cue (BF = 0.498) and a stress cue. The sensitivity analysis did not change those results.

Figure 3a illustrates time-to-cocaine relapse during the follow-up. The risk of cocaine relapse in the CBD and placebo groups was similar (HR = 1.20, CI = 0.65 to 2.20; $P = 0.512$; BF = 0.152). The median times-to-cocaine relapse were 4 days for the CBD group and 7 days for the placebo group. Those results were mostly unchanged following the sensitivity analysis (HR = 1.28, CI = 0.74 to 2.22; $P = 0.382$; BF = 0.119). Because only three participants did not relapse (CBD, *n* = one of 34, 2.9%; placebo, *n* = two of 27, 7.4%), the logistic regression analysis did not provide any meaningful results. Among participants who successfully completed detoxification and entered Phase II, six participants (CBD, *n* = four of 34, 11.8%; placebo, *n* = two of 27, 7.4%) relapsed because of missing data. The proportion of participants reaching sustained abstinence was similar between groups (CBD, *n* = seven of 34,

TABLE 1 Demographic and baseline characteristics of participants entering Phase I.

Characteristic		*Treatment group*		
		CBD (n = 40)	*Placebo (n = 38)*	*Total (n = 78)*
Age, mean (SD), years		46.0 (10.7)	45.8 (11.8)	45.9 (11.2)
Female sex, *n* (%)		7 (17.5)	7 (18.4)	14 (17.9)
Weight, mean (SD), kg		75.5 (13.7)	76.4 (18.4)	76.0 (16.1)
Body mass index, mean (SD), kg/m^2		25.3 (4.5)	25.5 (4.9)	25.4 (4.7)
Time between study initiation and last cocaine use, mean (SD), days		2.9 (3.1)	3.3 (3.6)	3.1 (3.3)
Frequency of cocaine use in the 2 weeks prior to study initiation, mean (SD), days		7.8 (4.9)	7.5 (4.5)	7.6 (4.7)
SDS total score, mean (SD)		11.2 (2.3)	11.6 (2.5)	11.4 (2.4)
SDS group, *n* (%)				
	Low (SDS < 10)	10 (25.0)	7 (18.4)	17 (21.8)
	High (SDS ≥ 10)	30 (75.0)	31 (81.6)	61 (78.2)
CUD severity based on the SCID, *n* (%)				
	Severe	36 (90)	37 (97.4)	73 (93.6)
	Moderate	4 (10)	1 (2.6)	5 (6.4)
Preferred route of cocaine administration, *n* (%)				
	Nasal	8 (20)	16 (42.1)	24 (30.8)
	Smoking	25 (62.5)	18 (47.4)	43 (55.1)
	Non-intravenous injection	1 (2.5)	0 (0.0)	1 (1.3)
	Intravenous	6 (15.0)	4 (10.5)	10 (12.8)
Highest level of schooling completed, *n* (%)				
	Less than high school	14 (35.0)	11 (28.9)	25 (32.1)
	High school	12 (30.0)	16 (42.1)	28 (35.9)
	More than high school	14 (35.0)	11 (28.9)	25 (32.1)
Ethnicity, *n* (%)				
	White	34 (85.0)	33 (86.8)	67 (85.9)
	Other	6 (15.0)	5 (13.2)	11 (14.1)
Employment status, *n* (%)				
	Full time	17 (42.5)	13 (34.2)	30 (38.5)
	Part time	7 (17.5)	10 (26.3)	17 (21.8)
Disability or employment insurance		2 (5.0)	7 (18.4)	9 (11.5)
	Social welfare	10 (25.0)	6 (15.8)	16 (20.5)
	Unstable condition	4 (10.0)	2 (5.3)	6 (7.7)
Marital status, *n* (%)				
	Married or common-law couple	1 (2.5)	2 (5.3)	3 (3.8)
	Single	39 (97.5)	36 (94.7)	75 (96.2)
Housing status, *n* (%)				
	Stable housing	32 (80.0)	33 (86.8)	65 (83.3)
	Homeless	8 (20.0)	5 (13.2)	13 (16.7)
Current substance use disorder, *n* (%)		14 (35.0)	10 (26.3)	24 (30.8)
	Cannabis	6 (15.0)	4 (10.5)	10 (12.8)
	Alcohol	5 (12.5)	4 (10.5)	9 (11.5)
	Stimulant	2 (5.0)	2 (5.3)	4 (5.1)
	Other	3 (7.5)	0 (0.0)	3 (3.8)

CBD = cannabidiol; CUD = cocaine use disorder; *n* = number of participants; SCID = structured clinical interview for DSM-V; SD = standard deviation; SDS = severity of dependence scale.

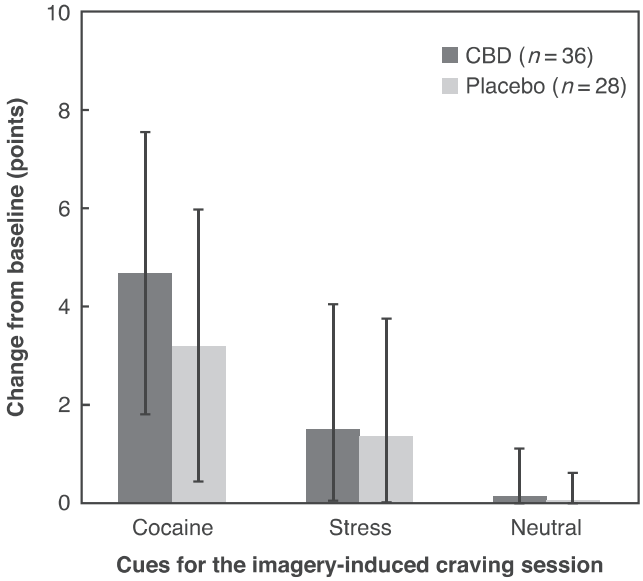


FIGURE 2 Cocaine craving among treatment groups. Bar chart illustrating mean changes in craving scores on the 10-point visual analogue scale in each treatment group following a cocaine, a stress and a neutral cue imagery-induced craving session. Standard deviations are indicated on the bars with vertical lines. CBD = cannabidiol; *n* = number of participants

TABLE 2 Results in each treatment group.

	Treatment group			
	CBD	*Placebo*	*CI*	*P-value*
Phase I, *n*	36	28		
Changes from baseline scores on the VAS for craving following imaginary scenarios				
Drug cue, mean (SD)	4.69 (2.89)	3.21 (2.78)	−0.16 to 3.12	0.069
Stress cue, mean (SD)	1.50 (2.56)	1.46 (2.32)	−1.20 to 1.27	0.887
Neutral cue, mean (SD)	0.14 (0.96)	0.04 (0.58)	−0.31 to 0.51	0.222
Phase II, *n*	34	27		
Participants reaching sustained abstinence, mean (SD)	20.6 (41.0) %	40.7 (50.1) %	−43.5 to 3.2%	0.089
Positive urine samples for cocaine, mean (SD)	68.1 (34.3) %	61.4 (36.1) %	−11.4 to 24.8%	0.461
Days with cocaine use over 92 days, mean (SD)	31.6 (29.6) %	28.6 (25.4) %	−11.4 to 17.3%	0.682

CBD = cannabidiol; *n* = number of participants; SD = standard deviation; VAS = visual analogue scale.

20.6%; placebo, *n* = 11 of 27, 40.7%). Figure 3b shows similar mean [standard deviation (SD)] cocaine use among groups during the follow-up period [CBD, 68.1 (34.3)%; placebo, 61.4 (36.1)%].

Supporting information, Figure S1 illustrates similar cocaine craving and withdrawal symptoms over time in both treatment groups.

Table 3 presents all drug-related AE and SAE. In the CBD group, 17 of 40 (42.5%) participants reported at least one AE related to the medication according to a blinded study physician. The most frequent AE included diarrhoea (*n* = 14 of 40, 35.0%) and nausea (*n* = three of 40, 7.5%).

During Phase I, 36 of 40 (90.0%) participants in the CBD group and 28 of 38 (73.7%) participants in the placebo group received all their doses. During Phase II, an average of 89.8% bottles were returned weekly at the pharmacy in the CBD group compared with 95.2% in the placebo group. The quantity of medication left in the bottles indicates that participants took the expected amount of medication. Figure 4 shows participants' CBD blood levels.

During Phase I, 25 of 40 (62.5%) and 23 of 38 (60.5%) participants in the CBD and placebo groups, respectively, attended at least one group therapy session. During Phase II, these prevalences decreased to 12 of 34 (35.3%) and 14 of 27 (51.9%), respectively. During the study, 65 of 78 (83.3%; CBD, *n* = 37 of 40, 92.5%; placebo, *n* = 28 of 38, 73.7%) participants took another medication at least once. During Phase II, 56 of 61 (91.8%; CBD, *n* = 33 of 34, 97.1%; placebo, *n* = 23 of 27, 85.2%) participants consumed at least one other substance (Supporting information, Table S2).

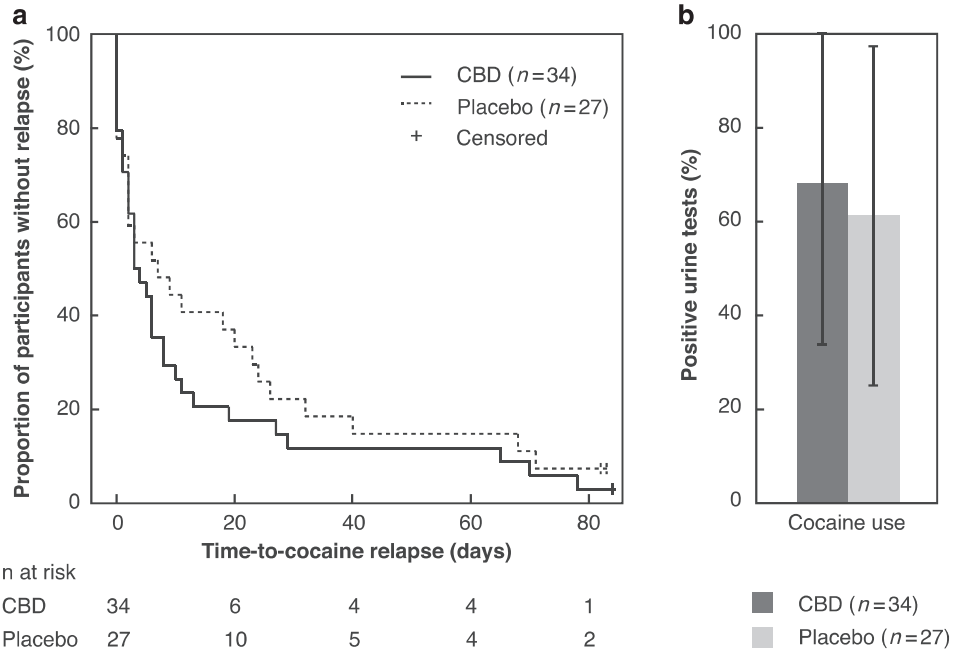


FIGURE 3 Time-to-cocaine-relapse and cocaine use among treatment groups. (a) Kaplan–Meier curves illustrating the proportion of participants without cocaine relapse in each treatment group during the 12-week follow-up period (Phase II) together with the number of participants at risk of relapse. (b) Bar chart illustrating similar cocaine use in both treatment groups during the follow-up period. Standard deviations are indicated on the bars with vertical lines. CBD = cannabidiol; *n*= number of participants

TABLE 3 Adverse events related to the medication during both phases.

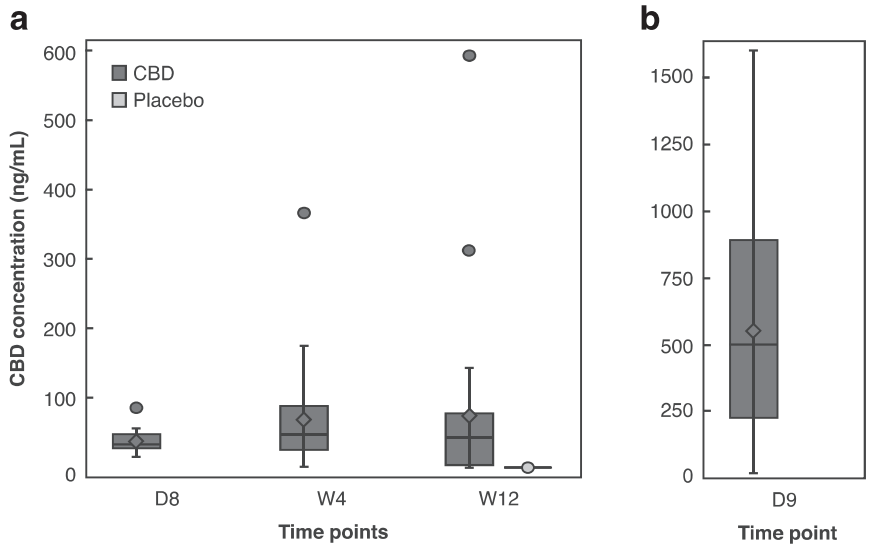
	Treatment group					
	CBD (n = *40*)		*Placebo* (n = *38*)		*Total* (n = *78*)	
Preferred term	*Event*	*Subject (%)*	*Event*	*Subject (%)*	*Event*	*Subject (%)*
Diarrhoea	26	14 (35.0)	1	1 (2.6)	27	15 (19.2)
Nausea	3	3 (7.5)	3	2 (5.3)	6	5 (6.4)
Abdominal pain upper	3	2 (5.0)	0	0 (0.0)	3	2 (2.6)
Hypoaesthesia	2	1 (2.5)	1	1 (2.6)	3	2 (2.6)
Abdominal distension	0	0 (0.0)	2	2 (5.3)	2	2 (2.6)
Insomnia	2	2 (5.0)	0	0 (0.0)	2	2 (2.6)
Dry mouth	0	0 (0.0)	1	1 (2.6)	1	1 (1.3)
Dizziness	1	1 (2.5)	0	0 (0.0)	1	1 (1.3)
Headache	0	0 (0.0)	1	1 (2.6)	1	1 (1.3)
Migraine	1	1 (2.5)	0	0 (0.0)	1	1 (1.3)
Tremor	0	0 (0.0)	1	1 (2.6)	1	1 (1.3)
Pruritus	1	1 (2.5)	0	0 (0.0)	1	1 (1.3)
Rash	1	1 (2.5)	0	0 (0.0)	1	1 (1.3)
Fatigue	0	0 (0.0)	1	1 (2.6)	1	1 (1.3)
Blood creatinine increased	0	0 (0.0)	1	1 (2.6)	1	1 (1.3)
Nasal dryness	0	0 (0.0)	1	1 (2.6)	1	1 (1.3)
Hepatitis*	0	0 (0.0)	1	1 (2.6)	1	1 (1.3)

CBD = cannabidiol; *n* = number of participants; *serious adverse event.

In the CBD group, 13 of 27 (48.1%) study completers correctly guessed their treatment allocation compared with nine of 23 (39.1%) study completers in the placebo group. The James blinding index was 0.563 (CI = 0.425–0.696), indicating that random guessing occurred.

DISCUSSION

Our study was timely, and much-needed in the context of increased interest regarding CBD to treat addiction. Similar cue-induced craving, daily craving, cocaine withdrawal



n				
CBD	36	28	24	36
Placebo	28	24	23	28

FIGURE 4 Participants' CBD blood levels among treatment groups. Box and whisker plots illustrating minimum, first quartile, median, third quartile and maximum CBD concentrations in each treatment group. Mean and outlier values are marked with diamonds and circles, respectively. In the CBD group, 9.00 a.m. CBD blood concentration evolved from (mean ± standard deviation) 37.14 ± 14.54 ng/ml on day 8 to 67.75 ± 71.20 ng/ml on week 4 and 74.57 ± 130.33 ng/ml on week 12. At 1.00 p.m. on day 9, CBD blood concentration was 553.82 ± 379.13 ng/ml in the CBD group. The single participant treated with placebo who tested positive for CBD had a CBD blood concentration of 0.06 ng/ml. CBD = cannabidiol; D = day; *n* = number of participants analyzed, including those with no detectable CBD; W = week

symptoms, sustained abstinence, cocaine use and time to relapse were observed in the CBD and placebo groups. Contrary to our hypothesis, our results do not support the superiority of CBD treatment compared with placebo for CUD.

A number of possible explanations for our negative findings on drug–cue-induced craving and time to relapse merit consideration. Although significant CBD blood levels were detected in all participants receiving CBD, questions remain as to the optimal dosage of CBD. CBD complex dose–response curves [22,40] suggest that both lower and higher doses could have led to different results. However, 300 mg of CBD did not decrease cocaine craving in individuals with CUD [24]. Furthermore, as CBD peak plasma concentration is approximately 3 hours after oral administration [41] and cocaine use can occur at any time, an administration twice instead of once daily may have been more effective to stabilize CBD plasma levels. That considered, CBD may simply not be sufficient as a stand-alone cannabinoid to reduce craving and prevent relapse in individuals with CUD. Alternatively, CBD might be efficacious in reducing craving and increasing time to relapse only for some substance use disorders (e.g. opioids) but not in others (e.g. stimulants). For example, CBD efficiently reduced heroin craving via visual attentional bias in individuals with HUD [21] and decreased cigarette consumption in tobacco smokers [42]. Furthermore, CBD could be efficacious in individuals with less severe substance use disorder or with demonstrated abstinence capabilities. In this study, we enrolled mostly severe individuals with CUD who had consumed cocaine in the past 2 weeks to undergo detoxification. This contrasts with the Hurd *et al.* study, in which nearly a third of participants had not consumed heroin for the past 2 months [21]. A recent pre-clinical study further supports that CBD efficiency may impact upon consumption of a small dose of cocaine but not a high dose [43].

In our study, CBD administration was safe, well tolerated and mainly associated with mild AE together with a few SAE. Participants in the CBD group mostly experienced diarrhoea and nausea, which is in line with previous findings [14,31]. However, we found a higher prevalence of diarrhoea in our CBD group compared with the literature reporting in only 17–19% of participants. Although our total daily dosage was similar to that of previous studies, we administered CBD once instead of twice daily, which could explain higher diarrhoea prevalence.

Several limitations should be considered while interpreting these results. First, our measures were mainly subjective, including time-to-cocaine relapse that used the TLFB to assess cocaine use outside the 3-day window covered by weekly urinalysis. Furthermore, participants knew when urine tests were scheduled and could potentially plan their cocaine use to avoid detection. There was also no direct supervision of medication intake during Phase II. Our cue-induced craving paradigm differed from other studies [21,23], which could limit our ability to compare our results. Also, our sample size was smaller than our

initial target, which reduced the statistical power to 56.4%. Moreover, our attrition rates of approximately 20% for both phases were higher than expected, although matching those of studies with similar populations [7]. Lastly, the existence of two primary outcomes and Bonferroni correction could have compromised our ability to detect a significant group difference, especially in the context of a premature end of recruitment. Despite these limits, BF values suggest that our results do not provide evidence for the superiority of CBD to decrease cocaine craving or relapse.

In conclusion, CBD was relatively well tolerated but not superior to placebo in reducing cocaine craving or increasing time-to-relapse. As opposed to other substance use disorders such as alcohol, opioids and nicotine, research endeavours have proved relatively disappointing in developing efficacious pharmacological intervention for people with CUD. More than ever there is a crucial need to identify new pharmacological and psychosocial interventions for the treatment of CUD.

Clinical trial registration

This study was registered with ClinicalTrials.gov (NCT02559167).

Declaration of interests

The Canadian Institutes of Health Research funded this study. The investigational product was provided by Insys Therapeutics. D.J.A. holds a scholar award from the Fonds de recherche du Québec en Santé. J.B. receives financial support from AbbVie and Gilead Sciences for work outside of this study. V.M.P., S.B., P.C., S.D., G.G. and E.S. report no financial relationship with commercial interests. The funder of the study or Insys Therapeutics had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Author contributions

Violaine Mongeau-Pérusse: Formal analysis; writing - original draft. **Suzanne Brissette:** Funding acquisition; investigation; methodology; writing - review and editing. **Julie Bruneau:** Conceptualization; funding acquisition; methodology; writing - review and editing. **Patricia Conrod:** Funding acquisition; methodology; writing - review and editing. **Simon Dubreucq:** Investigation; methodology; writing - review and editing. **Guillaume Gazil:** Data curation; formal analysis; writing - review and editing. **Emmanuel Stip:** Funding acquisition; methodology; writing - review and editing. **Didier Jutras-Aswad:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; writing - original draft.

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Supporting Information

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

Figure S1 Cocaine craving and withdrawal symptoms among treatment groups. Line charts illustrating similar mean cocaine craving scores according to (**A**) the CCQ-Brief ($P = 0.698$) and (**B**) the VAS ($P = 0.362$) together with (**C**) similar mean cocaine withdrawal symptoms scores as assessed by the CSSA test ($P = 0.662$) in both treatment groups. Standard deviations are indicated on the graph with vertical lines. CBD, cannabidiol; CCQ-Brief, Cocaine Craving Questionnaire Brief; CSSA, Cocaine Selective Severity Assessment; D, day; n, number of participants; VAS, Visual Analog Scale; W, week.

Table S1 Study timeline and assessment schedule.
Table S2 Substance consumption during phase II.