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ORIGINAL ARTICLE

Cannabidiol for the treatment of crack-cocaine craving: an exploratory double-blind study

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Objective: To assess the efficacy of cannabidiol (CBD) in the management of crack-cocaine craving and the treatment of frequent withdrawal symptoms.
Methods: Thirty-one men with a diagnosis of crack-cocaine dependence were enrolled in a randomized, double-blind, placebo-controlled trial. We applied neuropsychological tests and assessed craving intensity, anxiety and depression symptoms, and substance use patterns at baseline and at the end of the trial. The participants were treated with CBD 300 mg/day or placebo for 10 days. During this period, we used a technique to induce craving and assessed the intensity of symptoms before and after the induction procedure.
Results: Craving levels reduced significantly over the 10 days of the trial, although no differences were found between the CBD and placebo groups. Craving induction was successful in both groups, with no significant differences between them. Indicators of anxiety, depression, and sleep alterations before and after treatment also did not differ across groups.
Conclusion: Under the conditions of this trial, CBD was unable to interfere with symptoms of crack-cocaine withdrawal. Further studies with larger outpatient samples involving different doses and treatment periods would be desirable and timely to elucidate the potential of CBD to induce reductions in crack-cocaine self-administration.

Keywords: Crack-cocaine; craving; cannabidiol; dependence

Introduction

The use of illicit substances is a major public health problem that affects hundreds of millions people worldwide.[1] Exposure to crack-cocaine rapidly induces a pattern of compulsive use and dependence, which is associated with marked personal, social, and economic losses.[2,3] In Brazil, the prevalence of crack-cocaine use suggests that the country is amongst the biggest consumer markets of these drugs worldwide.[4]

Recurrent, severe craving and a high frequency of relapses are remarkable clinical features of crack-cocaine dependence. It should be noted that craving is a critical factor for the onset of compulsive use and dependence, and adds to the failure in remaining abstinent.[5,6] Craving measures have increasingly been used as a primary endpoint in clinical trials, as craving severity may predict relapse and treatment outcomes.[5,7-9] Different studies have demonstrated that stimuli previously associated with drug use can consistently induce craving in individuals with crack-cocaine dependence,[10] leading to the development of craving induction techniques (cue-induced craving) that can be used in the assessment of pharmacological interventions to treat dependence.[11,12]

Despite unquestionable advances in the understanding of neurobiological alterations associated with drug dependence in recent decades, there is no pharmacological treatment with proven efficacy in the treatment of crack-cocaine dependence.[13-15] Different sources of evidence have suggested that the dopaminergic neurotransmission system is involved in the reinforcing effects of cocaine addiction, and may mediate its onset and maintenance.[16-18] Furthermore, both preclinical and clinical studies have shown that cocaine withdrawal syndrome is associated with impaired dopamine function.[19-22]

Different studies have suggested that agonists of cannabinoid CB1 receptors increase the discharge of dopaminergic neurons in the ventral tegmental area, which

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project to the nucleus accumbens,[23] leading to an increase in extracellular dopamine levels in this structure.[24-27] This is probably an indirect effect that occurs via inhibition of GABA neurons, which results in tonic inhibition of dopaminergic neurons.[28]

The use of cannabinoids has been previously highlighted in uncontrolled observations as a strategy for reducing cocaine consumption and to reduce craving,[5,29,30] suggesting that these compounds may have a crucial clinical therapeutic role for the treatment of crack-cocaine dependence. However, most of these studies were conducted with cannabis *in natura* or whole-plant extracts, which limits their reproducibility and raises ethical issues due to the harmful effects of the drug. Moreover, none of these studies tested pure, pharmaceutical-grade cannabidiol (CBD) for the treatment of crack-cocaine dependence.

CBD is a component of *Cannabis sativa* that is devoid of both psychotomimetic and typical effects of the plant.[31-33] CBD inhibits the reuptake and enzymatic hydrolysis of anandamide[34] and thus increases the availability of this endogenous CB1 receptor agonist. In animals, CBD reversed dopamine depletion induced by 6-hydroxydopamine in a model of Parkinson's disease,[35] and has been shown to regulate stress response and compulsive behaviors by activating the 5-HT1A serotonergic receptor.[36] Moreover, CBD is an allosteric modulator at mu- and delta-receptors in the opioid system.[37] Recent articles suggested that CBD may be useful to treat addiction to several substances[17,38] including cannabis,[39,40] tobacco,[41,42] alcohol,[43,44] heroin,[45] and cocaine.[46-49]

Furthermore, CBD has demonstrated anxiolytic,[38,50-54] antidepressant,[55] and neuroprotective properties.[56] Although the mechanisms underlying the neuroprotective properties of CBD are still poorly understood, findings from different sources have suggested the involvement of multiple pharmacological targets, including CB1 and 5-HT1A receptors,[36,57] antioxidant properties,[58] modulation of proinflammatory cytokines,[59] and brain-derived neurotrophic factor (BDNF) expression.[60] Altogether, findings from preclinical and clinical studies suggest that CBD is involved in different mechanisms related to acquisition of addiction and compulsive drug-seeking behaviors.

The main aim of the present study is to evaluate the efficacy and tolerability of CBD in treatment of crack-cocaine dependence. We hypothesized that CBD would show effectiveness in reducing craving symptoms while having good tolerability.

Methods

This was a randomized, double-blind, placebo-controlled trial. The trial was carried out at a therapeutic community unit specializing in the treatment of substance-related disorders affiliated with Instituto Bairral de Psiquiatria, a hospital that receives patients from the Brazilian public health system (Itapira, state of São Paulo, Brazil).

Subjects

The sample consisted of male subjects aged 18 and older with a DSM-IV diagnosis of crack-cocaine dependence, assessed with the Structured Clinical Interview for DSM-IV axis I Disorders (SCID-CV),[61] who had achieved abstinence for a maximum of 30 days (ranging from 8 to 30 days) and agreed to participate by signing an informed consent form.

Patients with current major psychiatric comorbidity (per DSM-IV), chronic infectious diseases, on antidepressants or antipsychotics, with severe or unstable medical conditions (documented episode of acute illness or exacerbation requiring active treatment), a history of brain injury with loss of consciousness, a history of allergies or idiosyncratic reactions to *Cannabis sativa*, illiteracy, or functional illiteracy were excluded. Of the 65 subjects assessed for eligibility, 31 met the inclusion/exclusion criteria. These participants were randomly assigned to two groups (CBD, n=14; placebo, n=17).

Assessment instruments

The instruments used in the sample are listed below.

- Cocaine Craving Questionnaire – Brief (CCQ-Brief): Short version of the original CCQ, a 45-item questionnaire that assess the main dimensions of craving.[62,63] The CCQ-Brief comprises only those 10 items related to the desire dimension. Each item is scored on an analog scale from 0 to 7, ranging from fully disagree to fully agree. Higher scores indicate higher levels of craving.[64] In this study, we used a Portuguese version of the instrument adapted to assess crack-cocaine craving.[65]
- Minnesota Cocaine Craving Scale (MCCS): A self-rating scale with five items that measure the intensity, frequency, and duration of craving episodes, as well as the effects of medication on craving intensity. We used a version that was translated and adapted to Portuguese[66] and replaced cocaine craving with crack craving.
- Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).[67]
- Beck Depression Inventory (BDI).[68]
- Beck Anxiety Inventory (BAI).[69]
- Visual Analog Sleep Scales (VAS): A self-rating instrument that assesses sleep and wakefulness conditions over the preceding 24 hours. The instrument has 15 items presented as visual analog scales, with each item consisting of two opposite statements located at the two ends of a line.[70,71] The VAS is divided into three parts: 1) the sleep disturbance scale, composed of seven items that measure sleep fragmentation and latency; 2) the effectiveness scale, with five items assessing sleep quality and duration; and 3) the supplementation scale, consisting of three items covering additional sleep periods outside the main sleeping time. Different studies have identified dramatic alterations in sleep architecture associated with chronic use of cocaine, suggesting that sleep disturbances could be targetable neurophysiological abnormalities.[72-75] In addition, sleep deficits are associated both with clinical disorders and with impairments in cognitive function, which are supposedly associated with relapse.[76,77]
- UKU Side Effects Rating Scale (UKU-SERS): This is a detailed scale that assesses psychological, neurological,

and autonomic effects in drug trials, with each item scored between 0 (absent) and 3 (severe). The UKU-SERS has questions that evaluate causal relationships between the effects observed and the study medication, which are rated as improbable, possible, or probable, in addition to items assessing the interference with and consequences of side effects for the individual's health.[78]

Study drug

CBD capsules were prepared with 99.9% pure CBD powder (THC-Pharm, Frankfurt, Germany/STI-Pharm, Brentwood, UK) dissolved in corn oil.[54,79] The same amount of oil alone was used to make the placebo capsules. Both CBD (150 mg) and placebo were placed in identical gelatin capsules, and both treatments consisted of two capsules/day. The 300 mg/day dose was chosen on the basis of previous studies in human models of anxiety that show that this dose is within the therapeutic window of the inverted U-shaped dose-response curve of CBD,[80,81] as well as on a previous case study of an inpatient with heavy cannabis use and withdrawal symptoms who was successfully treated with this dose regimen.[39]

Preparation for the study

The staff in charge of the patients were informed about the procedures, objectives, rationale, and inclusion and exclusion criteria of the study. In addition, they received information concerning the use of concomitant medications and possible medical emergencies that might arise involving the study participants.

The research staff received training consisting of study discussions, presentation of the assessment instruments and neuropsychological tests to clarify possible doubts, discussions on adequate and inadequate attitudes by the investigators, and supervised pilot interviews. For the procedure of craving induction, we played a video (approximately 3 minutes long) showing places (areas of drug use known by users), scenes of real crack use, and objects related to crack use (crack rocks, handling of the drug, preparation of the pipe, other instruments involved in the use of crack-cocaine). In order to assess the adequacy of the methods to be used in the trial, we conducted a pilot study with four participants who completed all steps of the data collection: screening, baseline assessment, treatment (placebo), assessment of craving for 10 days, and final assessment.

Procedures

The first 5 days of hospitalization for the treatment of substance use consisted of adaptation and "detoxification" of the patients. Detoxification/abstinence were not confirmed with urine tests because participants were hospitalized throughout the entire period of study. During this period, potentially eligible participants were identified. The patients referred by the staff were invited to participate in the study, and those who provided informed consent to participate were enrolled. After an initial psychiatric interview, participants were assessed with the SCID-IV to confirm diagnosis of crack-cocaine dependence and whether the participant fulfilled the inclusion/exclusion criteria related to the diagnosis of Axis I disorders. At this point, participants included in the study completed the following assessment instruments: ASSIST, CCQ-Brief and MCCS, BDI and BAI, and the VAS.

In the next step, participants were randomly assigned to the treatment groups and started the 10-day treatment period with CBD or placebo. During treatment, crack-cocaine craving was assessed twice daily (before and after craving induction), at about the same time each day ($\pm$ 1 hour), with the CCQ-Brief and the MCCS. Craving was induced using standardized audiovisual stimuli (cue-induced craving) as described above, before assessment. Any significant events during the treatment period were recorded in the patients' medical files. After 10 days of treatment, participants underwent a final assessment with the same instruments used at baseline (CCQ-Brief and MCCS, BDI and BAI, VAS, and the UKU-SERS adverse effects assessment). All procedures were conducted individually by an experienced investigator. During the study, participants received group psychotherapy once a week, the standard psychosocial intervention provided by the institution.

Data treatment

Data were analyzed using the intention-to-treat principle, in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized trials. All analyses were performed in SPSS version 20.0. Statistical significance was set $p < 0.05$ (two-tailed) for all analyses.

Data were captured for all visits where craving was assessed with the CCQ-Brief and MCCS (baseline and days 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10). First, skewness and kurtosis were calculated to verify normality of data distribution, which was not confirmed. Thus, we performed all subsequent analyses by using nonparametric tests. Between-group comparisons involving clinical data (e.g., severity of anxiety and depression symptoms) were performed with the Mann-Whitney *U* test. Means ($\pm$ standard deviation [SD]) were used to summarize typical values for each group. Between-group comparisons involving categorical variables were performed by Fisher's exact test.

Assessment of crack-cocaine craving was based on the CCQ-Brief and MCCS total scores. Assessments were performed before and after craving induction each day to validate the cue-induced technique. The mean change from baseline to the day 10 endpoint on those scales was used as the primary outcome measure. Using an intention-to-treat sample, defined as all participants with at least one post-baseline craving assessment, efficacy for CBD vs. placebo was tested using a mixed-model repeated-measures analysis of variance (RMANOVA). The mixed-model approach allows for patients with incomplete data to be included, and utilizes the data that is available for all patients. Frequencies of the most common adverse events are reported if present in at least one subject in either of the study groups.

Ethics statement

The study protocol was approved by the Universidade Federal de São Paulo ethics committee (UNIFESP; process 0302/11). All participants agreed to participate by signing an informed consent form.

Results

Sample characteristics

Groups were matched for age, education, days of hospitalization, and frequency of crack-cocaine use. Most subjects reported a frequency of use higher than five times per week; the mean age at first exposure was 20 years (SD = 7.2), and the mean duration of crack-cocaine use was 12 years (SD = 6.7). Participants reported the use of alcohol, marijuana, and crack in the 3 months preceding the trial. Regarding alcohol and marijuana, most participants were not classified as dependent; however, many fell in the category of risky use. Only two subjects (one from each group) used medications during the trial. Both used benzodiazepines ''as needed.''

The sociodemographic and clinical characteristics of the sample are summarized in Table 1. The distribution with respect to hospitalization time and pattern of crack use are presented in Table 2. Problems related to the current use of psychoactive substances according to the ASSIST are summarized in Table 3.

Effects of treatment

Eleven subjects (79%) in the experimental group and 14 subjects (82%) in the control group completed the trial. The remaining subjects dropped out and abandoned the institution. Table 4 summarizes the results for baseline (before treatment) and final (after treatment) assessments with the BDI, BAI, and VAS.

The RMANOVA of CCQ-Brief scores showed a significant effect of time ($F_{10,230} = 16.174$; $p < 0.001$), but not of treatment ($F_{10,230} = 2.663$; $p = 0.116$) or time/treatment interaction ($F_{10,230} = 0.489$; $p = 0.897$). The MCCS also showed a significant effect of time ($F_{10,230} = 16.450$; $p < 0.001$), but not of treatment ($F_{10,230} = 2,460$; $p = 0.130$) or time/treatment interaction ($F_{10,230} = 1,580$; $p = 0.113$). The mean scores of the two scales are shown in Figure 1. We reanalyzed the data including cannabis use (amount) as a covariate. Effects of treatment and time/treatment interaction remained nonsignificant for both scales. There was a significant reduction in severity of symptoms of anxiety and depression in both groups, but improvements in the CBD group did not differ from placebo. Differences in VAS sleep scores were nonsignificant in the two groups.

Regarding CCQ-Brief scores, there was a significant effect for phase ($F_{1,21} = 7.792$; $p = 0.011$), but not for treatment ($F_{1,21} = 3.144$; $p = 0.091$) or the phase/treatment interaction ($F_{1,21} = 3.080$; $p = 0.094$). As shown in Figure 2, the procedure was successful in inducing craving in the two groups. However, differences between groups were nonsignificant. Findings for the craving induction procedure are shown in Figure 1.

The adverse events recorded using the UKU-SERS were sleepiness and increased sleep duration (five subjects in the experimental group and three in the control group; $p = 0.45$), nausea (two subjects in the experimental group and one in the control group; $p = 0.59$), and headache (two subjects in the experimental group and one in the control group; $p = 0.59$). All adverse events

Table 1 Sociodemographic characteristics of the study sample

Variable	Experimental group (n=14)	Control group (n=17)	Total (n=31)	p-value*
Age (mean [SD])	32.5 (6.9)	33.2 (6.9)	32.9 (6.8)	
Marital status				
Married/stable relationship	4 (28.6)	4 (23.5)	8 (25.8)	0.99
Single	7 (50)	10 (58.8)	17 (54.8)	
Divorced/widowed	3 (21.4)	3 (17.7)	6 (19.4)	
Education				
Primary education (1st-4th grade)	2 (14.3)	3 (17.7)	5 (16.1)	0.95
Primary education (5th-8th grade)	4 (28.6)	5 (29.4)	9 (29.0)	
Higher education (incomplete)	2 (14.3)	1 (5.9)	3 (9.7)	
Higher education (complete)	6 (42.9)	8 (47.1)	14 (45.2)	
Occupational status				
Self-employed/employed	7 (50.0)	9 (52.9)	16 (51.6)	0.99
Unemployed/on leave	7 (50.0)	8 (47.1)	15 (48.4)	
Socioeconomic class				
A	0.0	0.0	0.0	
B	3 (21.4)	4 (23.5)	7 (22.6)	0.15
C	9 (64.3)	9 (52.9)	18 (58.1)	
D	0.0	4 (23.5)	4 (12.9)	
E	2 (14.3)	0.0	2 (6.4)	

Data presented as n (%), unless otherwise specified.
SD = standard deviation.
* Mann-Whitney *U* test.

Table 2 Distribution of the two groups with respect to hospitalization time and pattern of crack use

Variable	Experimental group (n=14)	Control group (n=17)	Total (n=31)	p-value*
	(n = 14)	(n = 17)	(n = 31)	
Days of hospitalization	15.93 (4.7)	13.18 (5.2)	14.42 (5.1)	0.10
Previous hospitalizations				
No	1 (7.1)	6 (35.3)	7 (22.6)	0.99
Yes	13 (92.9)	11 (64.7)	24 (77.4)	
Number of hospitalizations	2.64 (1.9)	1.71 (3.1)	2.13 (2.7)	0.06
Medication use, current				
No	13 (92.9)	15 (88.2)	28 (90.3)	0.99
Yes	1 (7.1)	2 (11.8)	3 (9.7)	
Medication use, past				
No	14 (100.0)	16 (94.1)	30 (96.8)	0.99
Yes	0 (0.0)	1 (5.9)	1 (3.2)	
Age at onset of crack use	23.36 (7.8)	18.59 (6.0)	20.74 (7.2)	0.07
Quantity used (g/week)	11.64 (8.6)	12.65 (12.8)	12.19 (10.9)	0.99
Frequency of use (times/week)				
1-2	0 (0.0)	1 (5.9)	1 (3.2)	0.99
3-4	3 (21.4)	3 (17.7)	6 (19.4)	
> 5	11 (78.6)	13 (76.5)	24 (77.4)	

Data presented as mean (SD) or n (%).
SD = standard deviation.
* Mann-Whitney's *U* test.

Table 3 Distribution of problems related to the current use of psychoactive substances in the two groups according to the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Psychoactive substances	Experimental group (n=14)	Control group (n=17)	Total (n=31)	p-value*
Tobacco				
Low risk	5 (35.7)	4 (23.5)	9 (29.0)	0.36
Moderate risk	9 (64.3)	10 (58.8)	19 (61.3)	
High risk/dependence	0 (0.0)	3 (17.6)	3 (9.7)	
Alcohol				
Low risk	10 (71.4)	12 (70.6)	22 (71.0)	0.99
Moderate risk	2 (14.3)	2 (11.8)	4 (12.9)	
High risk/dependence	2 (14.3)	3 (17.6)	5 (16.1)	
Marijuana				
Low risk	11 (78.6)	7 (41.2)	18 (58.1)	0.07
Moderate risk	3 (21.4)	10 (58.8)	13 (41.9)	
Cocaine/crack				
High risk/dependence	14 (100.0)	17 (100.0)	31 (100.0)	

Data presented as n (%).
* Mann-Whitney's *U* test.

were of mild or moderate severity. No serious adverse event occurred during the trial. The frequency of adverse events did not differ between groups (p = 0.34).

Discussion

The results of this randomized, placebo-controlled trial suggest that, despite excellent safety and tolerability, CBD failed to demonstrate efficacy in the treatment of craving in subjects with crack-cocaine dependence. Despite these negative findings, to our knowledge, this is the first study examining the efficacy of CBD in the treatment of crack-cocaine dependence in humans.

Anxiety symptoms decreased significantly in both groups during the trial. Regarding depressive symptomatology, a significant reduction was found among participants in the control group, while the change in the experimental group only tended towards statistical

Table 4 Results for baseline and final assessments with the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and the Visual Analog Sleep Scales (VAS) in the two groups

Variable/group/time	n	Mean (SD)	p-value*	Difference from baseline to final, mean (SD)	Comparison between EG and CG (p-value)
Anxiety symptoms					
EG					
1	14	18.21 (11.6)	0.02*	-8.64 (9.6)	0.80
2	11	8.45 (6.6)			
CG					
1	17	15.94 (11.8)	< 0.01*	-8 (9.4)	
2	14	6.57 (8.5)			
Depressive symptoms					
EG					
1	14	18.64 (6.6)	0.06	-5.91 (7.6)	0.46
2	11	13.09 (8.0)			
CG					
1	17	17.06 (10.4)	< 0.01*	-8.5 (7.8)	
2	14	8.93 (8.4)			
Sleep disturbances					
EG					
1	14	26.91 (11.6)	0.99	-0.73 (15.5)	0.27
2	11	26.18 (18.2)			
CG					
1	17	26.57 (21.1)	0.27	-9.93 (21.2)	
2	14	16.64 (14.0)			
Sleep effectiveness					
EG					
1	14	9.27 (5.5)	0.40	3.73 (10.6)	0.37
2	11	13.00 (10.2)			
CG					
1	17	9.86 (11.4)	0.56	-1 (11.1)	
2	14	8.86 (9.3)			
Sleep supplementation					
EG					
1	14	5.64 (7.2)	0.77	-0.64 (8)	0.54
2	11	5.00 (6.0)			
CG					
1	17	4.71 (6.3)	0.07	-3.5 (6.5)	
2	14	1.21 (2.0)			

CG = control group; EG = experimental group; SD = standard deviation; time 1 = baseline assessment; time 2 = final assessment.
* Statistically significant difference.

significance. There were no differences between the experimental and control groups in terms of baseline and final assessments of anxiety and depression symptoms. This finding contrasts with studies reporting the efficacy of CBD in treating anxiety disorders.[53,55] However, such evidence mainly comes from preclinical studies in which CBD was administered acutely; evidence from clinical studies investigating chronic CBD use in anxiety disorders is limited.[82]

The results of the CCQ-Brief and the MCCS showed the presence of moderate to high severity of craving in both groups at first assessment, which decreased significantly over the 10 days of the trial. Between-group comparisons, however, showed no differences, suggesting that CBD treatment did not contribute to the reduction in craving severity. This suggests that the observation that use of cannabis facilitates abstinence from crack cocaine[83] cannot be attributed to CBD.

The decrease in craving intensity over the 10 days of the trial in the two groups does not seem to be related to the general treatment measures provided by the institution, since the experiment started, on average, 15 days after admission, and craving scores on the first day of the trial were high for both groups. In addition, decreases in anxiety and depressive symptomatology did not appear to be related to the resolution of withdrawal syndrome, since enrollment in the study occurred at 8 to 30 days of abstinence. Reductions in craving severity and significant decreases in anxiety and depression symptoms might be associated with a placebo effect related to the knowledge that subjects could be receiving a new medication, as well as to the individualized attention that patients received during the study period, with daily application of the assessment instruments. It may also have occurred due to the activities carried out at the facility, the general health care provided by the staff, the impossibility of using the drug during hospitalization, and of being away from the usual environment of drug use.

Different studies have shown that craving is an unstable condition affected by environmental, social, and emotional influences.[5,9] Similarly, the duration of abstinence and deprivation of liberty, which makes use and contact with

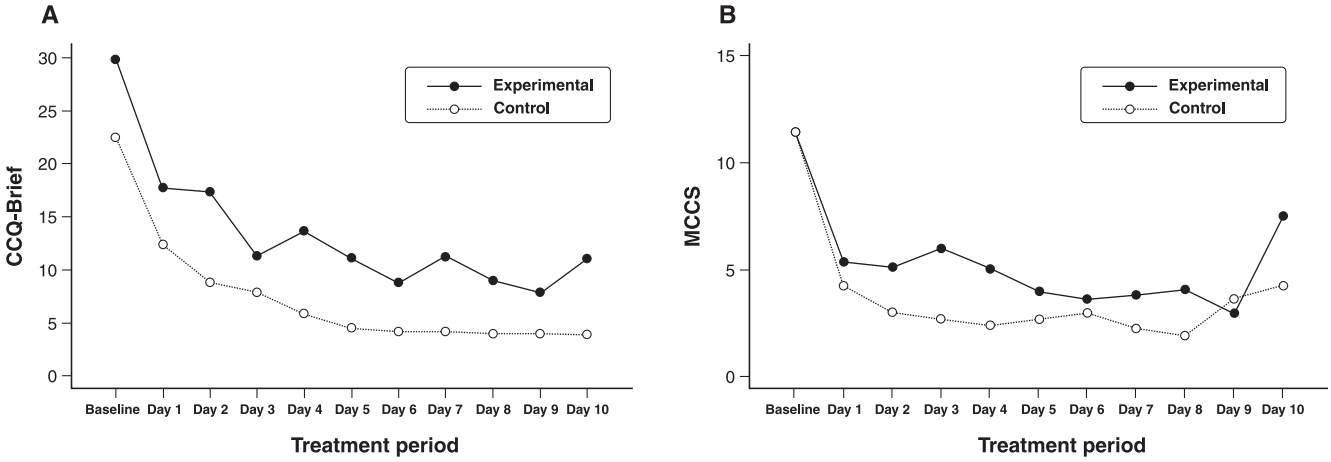

Figure 1 Craving levels assessed with A) the Cocaine Craving Questionnaire – Brief (CCQ-Brief) and B) the Minnesota Cocaine Craving Scale (MCCS) over the treatment period.

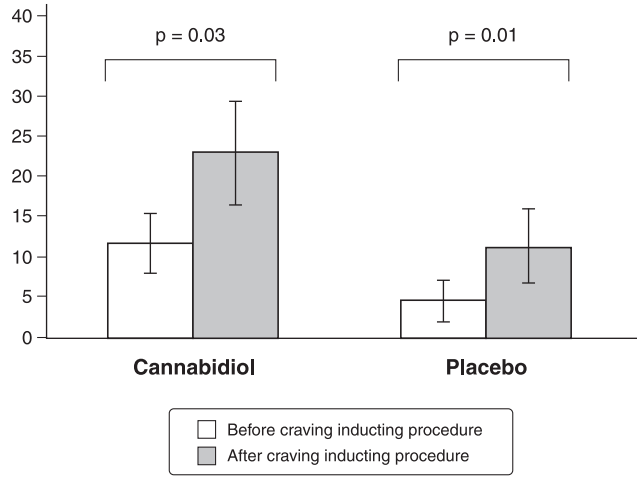

Figure 2 Cocaine Craving Questionnaire – Brief (CCQ-Brief) scores before and after the craving induction procedure.

drug-use environments difficult or even impossible, do not favor craving induction.[6] It should be noted that conditioned stimuli (such as seeing someone use crack, feeling the smell of the substance, handling paraphernalia, going to typical places of use) have consistently been described as triggers of craving among substance users.[4-6]

The use of a craving-inducing procedure in the present study increased craving intensity in the two groups, but with no significant differences between them. This finding is in line with a recent double-blind, placebo-controlled functional magnetic resonance imaging study in which CBD did not acutely affect the neural correlates of reward anticipation and feedback in healthy participants.[84] However, this observation contrasts with previous animal literature that consistently shows that the administration of CBD reduces self-administration, cocaine-seeking behaviors, and cocaine-induced reward; attenuates the central adaptations induced by cocaine; and changes contextual and emotional memories associated with cocaine, thus decreasing the amount of drug use.[47-49,85,86]

The main limitation of the present study was related to the treatment setting, since craving and withdrawal symptoms tend to be less severe and to decrease linearly in hospitalized patients, unlike in an outpatient setting where these symptoms tend to be more frequent, intense, and persistent. Additionally, different aspects of the intervention, including the short treatment period and the long interval between cessation of use and the start of the trial, might have contributed to the negative findings. The dose of CBD (300 mg/day) was relatively low, with no uptitration; since the effects of CBD are biphasic,[80] the use of a single dose also limits evaluation of the effectiveness of this cannabinoid. For instance, two recent double-blind placebo-controlled trials of CBD in subjects with heroin[45] and cannabis[40] use disorder, respectively, observed efficacy with the use of higher doses (400 and 800 mg).

Also, the tendency for the CBD group to have more previous hospitalizations, a fact that is usually associated with greater severity and increased substance use-related problems, might also have contributed to the absence of differences between the groups. Moreover, since the rates of psychiatric and infectious comorbidities are high among crack-cocaine users and may have influence treatment outcomes,[87] such exclusions in our study would have produced a highly artefactual sample. Thus, the study sample may not represent the general socioclinical profile of crack-cocaine users in general, and in Brazil in particular. Finally, type-II statistical error cannot be ruled out in view of the relatively small overall sample size, and may mean that the study was underpowered for conclusive insights or for adequate testing of interactions with other crucial factors.

Although these preliminary findings failed to show evidence of the efficacy of CBD in reducing craving in subjects with crack-cocaine dependence, further investigations that overcome the limitations described above are necessary. This is particularly true if we consider the excellent tolerability and safety profiles of CBD and the encouraging animal evidence of this cannabinoid as an adjunct therapy for the treatment of crack-cocaine

dependence.[7,88,89] Therefore, future double-blind, placebo-controlled, randomized clinical trials with larger, less selective samples and using different doses of CBD in outpatients are of particular interest to elucidate the potential of CBD to reduce self-administration of crack cocaine.

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Disclosure

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