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The interplay of cannabinoid and NMDA glutamate receptor systems in humans: Preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects

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ABSTRACT

Background: Interactions between glutamatergic and endocannabinoid systems may contribute to schizophrenia, dissociative states, and other psychiatric conditions. Cannabidiol (CBD), a cannabinoid-1/2 (CB1/2) receptor weak partial agonist or antagonist, may play a role in the treatment of schizophrenia.
Objective: This study tested the hypothesis that CBD would attenuate the behavioral effects of the NMDA receptor antagonist, ketamine, in healthy human subjects.
Methods: Ten male healthy volunteers were evaluated twice in a randomized order. In both sessions they received ketamine (bolus of 0.26 mg/kg/1 min followed by IV infusion of 0.25 mg/kg over 30 min) preceded by either CBD (600 mg) or placebo. Psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS) and the CADSS (Clinician Administered Dissociative States Scale) at regular intervals from 30 min before to 90 min after ketamine administration.
Results: CBD significantly augmented the activating effects of ketamine, as measured by the activation subscales of the BPRS. However, CBD also showed a non-significant trend to reduce ketamine-induced depersonalization, as measured by the CADSS.
Conclusion: These data describe a complex pattern of psychopharmacologic interactions between CBD and ketamine at the doses of each agent studied in this experiment.

1. Introduction

The potential therapeutic effects of cannabidiol (CBD), a major constituent of the *Cannabis sativa* plant, are being studied because it produces some desirable effects without the psychotomimetic effects associated with Δ9-tetrahydrocannabinol (Δ9-THC) (Zuardi et al., 1982). It produces a complex dose-dependent profile of pharmacologic effects as a consequence of its multiple mechanisms of action, such as a non-competitive antagonism of cannabinoid-1 (CB1) receptors and an inverse agonism of cannabinoid-2 (CB2) receptors (Pertwee, 2008; Thomas et al., 2007), blockade of anandamide uptake, and inhibition of the enzymatic hydrolysis of anandamide (Bisogno et al., 2001). CBD also has an agonist activity at 5-HT_{1A} receptors (Russo et al., 2005), decreases the uptake of [^{3}H] adenosine (Carrier et al., 2006), and stimulates vanilloid receptors (Bisogno et al., 2001). In animals, many effects of CBD exhibit a biphasic or bell-shaped dose–response relationship, including the anxiolytic, antiemetic, neuroprotective, anti-inflammatory and sedative effects (Zuardi, 2008). Its actions at CB2 receptors appear to account for its anti-inflammatory actions (Thomas et al., 2007; Malfait et al., 2000). In humans, THC produces many signs and symptoms associated with schizophrenia (D'Souza et al., 2004), while CBD has few behavioral effects other than sedation at high doses (Hollister, 1973; Consroe et al., 1991; Zuardi et al., 1993). Several reports suggest that CBD attenuates the anxiogenic,

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol; CB1, cannabinoid-1; CB2, cannabinoid-2; NMDA, N-methyl-D-aspartate; PPI, prepulse inhibition; SCID-NP, structured clinical interview for the DSM-non-patient edition; SPSS, Severity of Psychosocial Stressors Scale for adults; BPRS, Brief Psychiatric Rating Scale; SIG, structured interview guide; CADSS, Clinician Administered Dissociative States Scale; RMANOVA, repeated measures analysis of variance.

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cognitive, and perceptual effects of THC (Zuardi et al., 1982; Hollister, 1973; Perez-Reyes et al., 1973; Karniol and Carlini, 1973; Leweke et al., 1999; Russo and Guy, 2006). Although a potent and selective CB1 receptor antagonist failed to show efficacy in treating schizophrenia (Meltzer et al., 2004), there is preliminary evidence suggesting that CBD might enhance antipsychotic treatment in some patients (Zuardi et al., 1995, 2006).

Studying the interactive effects of CBD and ketamine might improve our understanding of the interplay of CB1/2 and N-methyl-D-aspartate (NMDA) receptor systems and guide later studies of CBD pharmacotherapy for schizophrenia. The administration of the NMDA receptor antagonist ketamine has been used to model deficits in the NMDA receptor function that might contribute to cognitive impairments and symptoms associated with schizophrenia and other disorders (Krystal et al., 1999, 2003). Drugs that reduced the cognitive and behavioral effects of ketamine, such as mGluR2/3 agonists, later showed efficacy in treating symptoms of schizophrenia (Krystal et al., 2005a,b; Patil et al., 2007). Preclinical studies suggest that CBD attenuates prepulse inhibition (PPI) deficits and stereotypy produced by NMDA receptor antagonists (Long et al., 2006; Moreira and Guimaraes, 2005), but not memory impairments (Fadda et al., 2006).

The present preliminary study investigated the interactive effects of CBD and ketamine in healthy human volunteers using a double-blind placebo-controlled design. In contrast to studies of the interplay of CBD and THC, the current findings suggest a complex pattern of interacting behavioral effects of CBD and ketamine, including reductions in depersonalization symptoms, but worsening of activation.

2. Materials and methods

2.1. Participants

Ten healthy male subjects ranging in age from 20 to 36 years were recruited and consisted of 2 ethnicities (7 white and 3 mixed) of which 8 were single and 2 were married. Education ranged from 11 to 16 years. The subjects were recruited from the community by public advertisement and were compensated for their participation.

They were informed about the general psychological actions of ketamine and CBD and their possible adverse effects. After providing informed consent in their native language, the subjects underwent a structured interview (SCID-NP) (Spitzer et al., 1990) translated into Brazilian Portuguese (Del-Ben et al., 1996) and completed the Severity of Psychosocial Stressors Scale for adults (SPSS — American Psychiatric Association, 1994). We obtained medical history, physical examination and laboratory testing for toxicology on all subjects. Exclusion criteria included current or previous history of psychiatric disorder and/or family history of Axis-I psychiatric disorder in first degree relatives, alcohol or other substance dependence (excluding nicotine dependence), current clinical disease and scores of three or more on the SPSS. The subjects were required to abstain from psychoactive substance use for at least four weeks before the experiment and a toxicological screening was carried out prior to each experimental session; none of the subjects smoked tobacco or had a history of habitual alcohol consumption.

2.2. Methods

The volunteers participated in two double-blind test days. The subjects were told not to consume any alcohol for 24 h and caffeine for at least 4 h before each visit to the laboratory. They were advised to have at least 6 h of sleep the night before the experiment and to have a normal breakfast. They were randomly divided into two groups of five subjects. Each participant was evaluated on two different occasions, 1 week apart. In the first session, after a 30-min period of adaptation, the subjects were given a single dose of oral CBD (600 mg) or placebo, in a double-blind procedure. The sessions were held in the morning (between 0800 and 1200) to minimize the effects of circadian variation. In the second session, an identical procedure was followed except that the remaining drug was administered (i.e. those given CBD in the first session received placebo in the second and vice versa). The subjects were informed that they would receive CBD and placebo, but they were not told in which order. The investigators were also blind to the content of the capsules. At 65 min after the intake of the capsules the subjects received an intravenous infusion of S-ketamine solution (Ketalar® — *Parke-Davis*) in 0.9% saline containing 0.26 mg/kg of the drug in bolus; subsequently, an infusion pump with ketamine solution (0.25 mg/kg) was administered for 30 min, on both test days. During the procedure continuous electrocardiogram and automatic blood pressure measures were assessed. This time schedule was designed to allow CBD to reach its peak blood level. The behavioral and subjective effects of ketamine and CBD were assessed using the version of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) modified by Bech (Bech et al., 1986) and translated into Brazilian Portuguese (Zuardi et al., 1994). The BPRS was divided into four factors: negative, positive, anxiety/depression and psychomotor activation (Crippa et al., 2002). The interviews were performed by one of the authors using a structured interview guide (SIG), which has been shown to enhance test–retest reliability of the BPRS (Crippa et al., 2001). We also administered the Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998), translated into Portuguese specifically for this trial. The CADSS comprises 19 subjective items, divided into 3 components: depersonalization (items 3 to 7), derealization (items 1, 2, 8–13, 16–19) and amnesia (items 14 and 15). Both scales were applied immediately before the CBD or placebo ingestion and 65 min after CBD or placebo administration (prior to ketamine infusion). The BPRS was administrated 5, 30, 60, 90 and 120 min after administration of ketamine, and the CADSS was administered 90 min after the ketamine bolus.

3. Data analysis

The blood pressure and heart rate data were analysed using a two-factor repeated measures analysis of variance (RMANOVA) with Greenhouse–Geiser corrections to the degrees of freedom to correct for a lack of sphericity. The factors analysed were group (CBD or placebo), time and the group by time interaction. The BPRS total and factor scores were analysed using the nonparametric method of Brunner (Brunner et al., 2002) for group, time and group by time interaction. The CADSS total and factor results were evaluated comparing the scores before and after ketamine administration, using paired t-tests. For the BPRS and CADSS factors we conducted post-hoc tests, adjusting the significance level for the number of factors of each test.

4. Results

Of the 10 selected subjects, one was excluded from CADSS analyses (due to nausea and vomiting) before the last response of this scale.

4.1. Physiological measures

RMANOVA revealed significant time effects for systolic ($F_{45,5} = 17.4$; $p<0.001$) and diastolic ($F_{45,5} = 17.6$; $p<0.001$) blood pressures and heart rate ($F_{45,5} = 12.7$; $p<0.001$), indicating that ketamine significantly increased these physiological measures. There were no significant group effects on systolic ($F_{9,1} = 1.0$; $p = 0.347$) and diastolic ($F_{9,1} = 3.2$; $p = 0.105$) blood pressures, indicating that there were no differences between the CBD or the placebo pretreatment. There were no significant group by time interactions for either measure ($F_{45,5} = 0.8$; $p = 0.537$ and $F_{45,5} = 0.3$; $p = 0.916$, respectively). Similarly, there was no heart rate difference between the CBD and the placebo pretreatment, (drug effect:

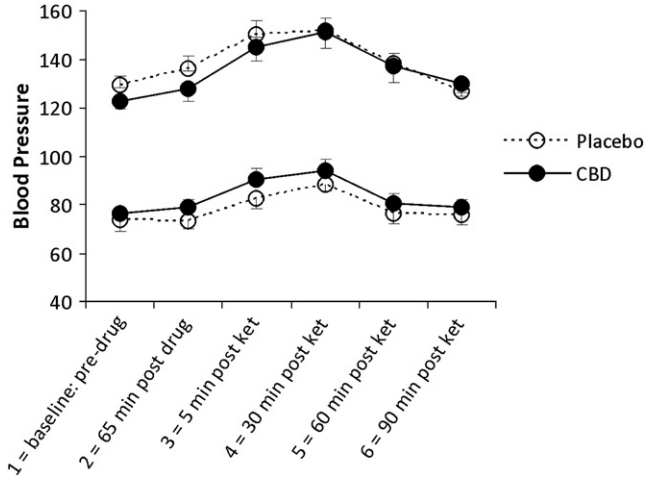

Fig. 1. Systolic and diastolic blood pressure means for the two groups (placebo and CBD) over time.

$F_{9,1} = 0.1$; $p = 0.731$) or group by time interaction ($F_{45,5} = 0.3$; $p = 0.931$). The mean values of blood pressure were shown in Fig. 1 and of heart rate in Fig. 2.

4.2. BPRS

The results of the BPRS total score using Brunner's method for analysis did not reveal significant drug by time interactions (ATS = 1.83; $p = 0.143$). The results for each of the BPRS factors are presented in Table 1. Significant time effects were observed for the four factors of the BPRS, indicating that ketamine increased all of these BPRS symptoms. A significant group effect was observed for the anxiety factor indicating that the average of scores over time was higher for CBD. At all time points there was a significant difference between the two groups. The only significant interaction (group by time) effect was observed for the activation factor, with a significantly higher CBD score at 30 min after ketamine (ATS = 6.56; $p = 0.03$ — Fig. 3).

4.3. CADSS

The CADSS results and analyses are presented in Table 2. There was no significant difference between placebo and CBD for the total CADSS score. Post-hoc testing of the three CADSS factor scores was conducted, adjusting for multiple comparisons. This analysis revealed a non-significant trend for CBD to decrease ketamine-induced depersonalization, without significant effects on derealization or amnesia.

Table 1
Brunner's analysis results for each of the BPRS factors.

BPRS	Effect	Num Df	ATS	P-value[1]
Anxiety factor	Group	1	7.45	0.0252*
	Time	3.06	6.1	0.0012*
	Group*Time	2.15	1.14	NS
Negative factor	Group	1	0.09	NS
	Time	1.97	46.72	<.0001*
	Group*Time	3.06	1.15	NS
Positive factor	Group	1	0.94	NS
	Time	2.21	47.6	<.0001*
	Group*Time	2.58	2.41	NS
Activation factor	Group	1	2.74	NS
	Time	2.73	5.94	0.0032*
	Group*Time	2.48	3.41	0.095+

[1]Adjusted for multiple comparisons; *significant; +non-significant trend; NS non-significant.

5. Discussion

The principal finding of this study was that CBD increased psychomotor activation produced by ketamine, but showed a non-significant trend to reduce ketamine-induced depersonalization in healthy human subjects. This study replicated previous findings that CBD had limited behavioral effects at the dose studied. It also replicated prior studies describing the production of positive and negative symptoms associated with schizophrenia by ketamine in healthy humans (Krystal et al., 1994). There were no significant interactive effects of CBD and ketamine on blood pressure, heart rate, positive symptoms and negative symptoms.

The ability of CBD to increase the psychomotor activation produced by ketamine is not well understood. The study design employed did not permit a careful evaluation of the possible stimulating effects of CBD, because ketamine was administered on all test days. However, both before and after ketamine effects emerged, CBD did not appear to markedly affect BPRS activation factor scores. Prior evidence suggested a relatively weak stimulatory effect of CBD in humans, where CBD was reported to increase feelings of being "clear-minded" and "quick-witted" (Zuardi et al., 1982). In this prior study, the weak stimulatory effects of CBD contrasted with the sedative effects of THC.

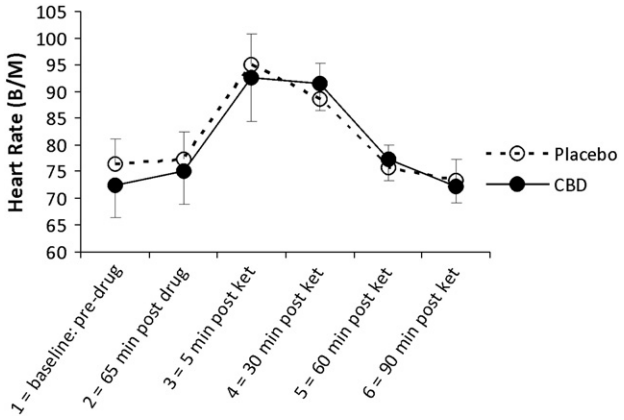

Fig. 2. Heart rate means for the two groups (placebo and CBD) over time.

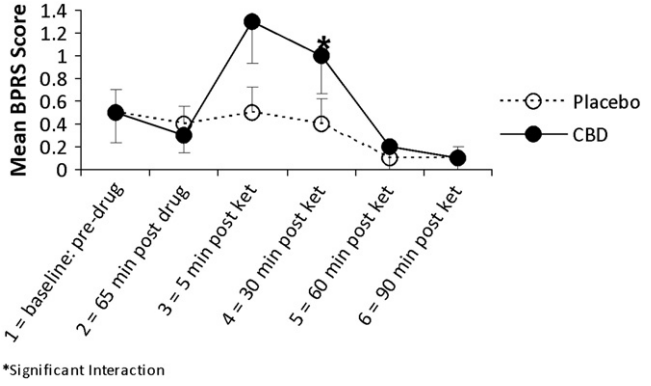

Fig. 3. BPRS activation factor scores for the two groups (placebo and CBD) over time. * indicates statistical significance with $p \leq 0.05$, data are presented as means and standard error of the means.

Table 2
Mean [Std error] of total CADSS and factor scores.

Variable	Placebo		CBD		Paired t-test[1]
Total CADSS	40	[5.34]	31.11	[6.05]	$t(8) = 1.51$, NS
Depersonalization	10.22	[1.65]	6.67	[1.33]	$t(8) = 2.64$, $p = .09^{+}$
Derealization	25.22	[3.13]	22.11	[3.62]	$t(8) = 0.87$, NS
Amnesia	4.56	[0.9]	3.22	[0.8]	$t(8) = 1.30$, NS

[1]Adjusted for multiple comparisons; $^{+}$non-significant trend; NS non-significant.

The preliminary evidence that CBD reduced depersonalization symptoms induced by ketamine merits further study. CBD has shown preliminary evidence of enhancing the treatment of schizophrenia (Zuardi, 2008) and attenuating THC-induced depersonalization (Zuardi et al., 1982). Lamotrigine, an anticonvulsant that reduced ketamine-induced depersonalization (Anand et al., 2000), also showed some efficacy in reducing depersonalization symptoms in some patients, although it was ineffective in a randomized trial (Sierra et al., 2001, 2003).

The ability to draw inferences from this study is reduced by a number of limitations in the study design. First, the small sample size of this preliminary investigation reduced the statistical power of most analyses. As a result, this study conducted exploratory post-hoc analyses even when they were not justified by the interaction of group and time effects. Second, this study employed single doses of CBD and ketamine, and, as a result, may have missed doses of CBD that had more pronounced or more uniform effects on ketamine responses. While this study is exploratory and the sample size is limited the study provides the necessary data to do an appropriate statistical power analysis in a future confirmatory investigation.

Ketamine and CBD have effects on glutamate and GABA release that may have contributed to the complex pattern of interactive behavioral effects in this study. For example, ketamine reduces the activation of GABA neurons and stimulates glutamate release in animals at doses comparable to those employed in the current study (Grunze et al., 1996; Moghaddam et al., 1997; Krystal et al., 2005a,b). Drugs that attenuate glutamate release tend to reduce positive (Krystal et al., 2005a,b) and in some cases negative (Anand et al., 2000) symptoms in humans. CBD would be expected to have complex effects on both the GABA and the glutamate release. CB1 receptors inhibit both the glutamate (Godino et al., 2007) and the GABA (Neu et al., 2007) release in the brain. These CB1 receptors are stimulated normally not only by endocannabinoids that are released by postsynaptic neurons in response to NMDA receptor stimulation, but also by other mechanisms (Beierlein and Regehr, 2006). CBD is an antagonist of CB1 receptor agonists, therefore it should block the effects of endocannabinoids upon glutamate and GABA release, but at the same time, it can also inhibit endocannabinoid uptake and hydrolysis besides other effects on serotonergic, adenosinergic and vanilloid systems. The complex interactive effects of ketamine and CBD and the relatively small simple size in this study suggest that additional research will be needed to characterize the interactive effects of these drugs in cortical circuits underlying cognition and psychosis.

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References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders4th edition. . Washington, DC: Author; 1994.
Anand A, Charney DS, Oren DA0, et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry 2000;57(3):270–6.
Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. Acta Psychiatr Scand Suppl 1986;326:1-37.
Beierlein M, Regehr WG. Local interneurons regulate synaptic strength by retrograde release of endocannabinoids. J Neurosci 2006;26(39):9935–43.
Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001;134(4):845–52.
Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress 1998;11(1): 125–36.
Brunner E, Domhof S, Langer F. Nonparametric analysis of longitudinal data in factorial experiments. New York (NY): John Wiley and Sons; 2002.
Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci USA 2006;103(20):7895–900.
Consroe P, Laguna J, Allender J, et al. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav 1991;40(3):701–8.
Crippa JA, Sanches RF, Hallak JE, et al. A structured interview guide increases brief psychiatric rating scale reliability in raters with low clinical experience. Acta Psychiatr Scand 2001;103(6):465–70.
Crippa JA, Sanches RF, Hallak JE, et al. Factor structure of Bech's version of the brief psychiatric rating scale in Brazilian patients. Braz J Med Biol Res 2002;35(10): 1209–13.
D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 2004;29(8):1558–72.
Del-Ben CM, Rodrigues CR, Zuardi AW. Reliability of the Portuguese version of the structured clinical interview for DSM-III-R (SCID) in a Brazilian sample of psychiatric outpatients. Braz J Med Biol Res 1996;29(12):1675–82.
Fadda P, Robinson L, Fratta W, et al. Scopolamine and MK801-induced working memory deficits in rats are not reversed by CBD-rich cannabis extracts. Behav Brain Res 2006;168(2):307–11.
Godino Mdel C, Torres M, Sanchez-Prieto J. CB1 receptors diminish both ca(2+) influx and glutamate release through two different mechanisms active in distinct populations of cerebrocortical nerve terminals. J Neurochem 2007;101(6): 1471–82.
Grunze HC, Rainnie DG, Hasselmo ME, et al. NMDA-dependent modulation of CA1 local circuit inhibition. J Neurosci 1996;16(6):2034–43.
Hollister LE. Cannabidiol and cannabinol in man. Experientia 1973;29(7):825–6.
Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. Psychopharmacologia 1973;33(1):53–70.
Krystal JH, Abi-Saab W, Perry E, et al. Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology (Berl) 2005a;179(1):303–9.
Krystal JH, D'Souza DC, Mathalon D, et al. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 2003;169(3–4):215–33.
Krystal JH, D'Souza DC, Petrakis IL, et al. NMDA agonists and antagonists as probes of glutamatergic dysfunction and pharmacotherapies in neuropsychiatric disorders. Harv Rev Psychiatry 1999;7(3):125–43.
Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994;51(3):199–214.
Krystal JH, Perry Jr EB, Gueorguieva R, et al. Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch Gen Psychiatry 2005b;62(9):985–94.
Leweke FM, Schneider U, Thies M, et al. Effects of synthetic delta9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. Psychopharmacology (Berl) 1999;142(3):230–5.
Long LE, Malone DT, Taylor DA. Cannabidiol reverses MK-801-induced disruption of prepulse inhibition in mice. Neuropsychopharmacology 2006;31(4):795–803.
Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci USA 2000;97(17):9561–6.
Meltzer HY, Arvanitis L, Bauer D, et al. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. Am J Psychiatry 2004;161(6):975–84.

Moghaddam B, Adams B, Verma A, et al. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 1997;17(8):2921–7.
Moreira FA, Guimaraes FS. Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. Eur J Pharmacol 2005;512(2–3):199–205.
Neu A, Foldy C, Soltesz I. Postsynaptic origin of CB1-dependent tonic inhibition of GABA release at cholecystokinin-positive basket cell to pyramidal cell synapses in the CA1 region of the rat hippocampus. J Physiol 2007;578(Pt 1):233–47.
Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799–812.
Patil ST, Zhang L, Martenyi F, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. Nat Med 2007;13(9):1102–7.
Perez-Reyes M, Timmons MC, Davis KH, et al. A comparison of the pharmacological activity in man of intravenously administered delta9-tetrahydrocannabinol, cannabinol, and cannabidiol. Experientia 1973;29(11):1368–9.
Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008;153(2):199–215.
Russo EB, Burnett A, Hall B, et al. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res 2005;30(8):1037–43.
Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses 2006;66(2):234–46.
Sierra M, Phillips ML, Ivin G, et al. A placebo-controlled, cross-over trial of lamotrigine in depersonalization disorder. J Psychopharmacol 2003;17(1):103–5.
Sierra M, Phillips ML, Lambert MV, et al. Lamotrigine in the treatment of depersonalization disorder. J Clin Psychiatry 2001;62(10):826–7.
Spitzer RL, Williams JR, Gibbson M, First MB. Structural clinical interview for DSM-III-R—Non-Patient edition (SCID-NP). Washington (DC): American Psychiatric Press; 1990.
Thomas A, Baillie GL, Phillips AM, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol 2007;150(5):613–23.
Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev Bras Psiquiatr 2008;30(3):271–80.
Zuardi AW, Guimaraes FS, Moreira AC. Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. Braz J Med Biol Res 1993;26(2):213–7.
Zuardi AW, Hallak JE, Dursun SM, et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol 2006;20(5):683–6.
Zuardi AW, Loureiro SR, Rodrigues CRC, Correa AJ, Glock SS. Estudo da estrutura fatorial, fidedignidade e validade da tradução e adaptação para o português da Escala de Avaliação Psiquiátrica Breve (BPRS) Modificada. Rev ABPAPAL 1994;16:63–8.
Zuardi AW, Morais SL, Guimaraes FS, et al. Antipsychotic effect of cannabidiol. J Clin Psychiatry 1995;56(10):485–6.
Zuardi AW, Shirakawa I, Finkelfarb E, et al. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology (Berl) 1982;76(3):245–50.