Therapeutical use of the cannabinoids in psychiatry

Uso terapêutico dos canabinoides em psiquiatria

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Abstract

Objective: *To review the main advances related to the potential therapeutic use of cannabinoid compounds in psychiatry.* ***Method:*** *A search was performed in the online databases PubMed, ScieELO, and Lilacs for studies and literature reviews concerning therapeutic applications of cannabinoids in psychiatry, especially cannabidiol, rimonabant, Δ^9-tetrahydrocannabinol, and their analogues.* ***Results:*** *Cannabidiol was found to have therapeutic potential with antipsychotic, anxiolytic, and antidepressant properties, in addition to being effective in other conditions. Δ^9-tetrahydrocannabinol and its analogues were shown to have anxiolytic effects in the treatment of* cannabis *dependence and to function as an adjuvant in the treatment of schizophrenia, although additional studies are necessary to support this finding. Rimonabant was effective in the treatment of the subjective and physiological symptoms of* cannabis *intoxication and functioned as an adjuvant in the treatment of tobacco addiction. The potential to induce adverse reactions such as depression and anxiety restrained the clinical use of this CB_1 antagonist.* ***Conclusion:*** *Cannabinoids may be of great therapeutic interest to psychiatry; however, further controlled trials are necessary to confirm the existing findings and to establish the safety of such compounds.*

Descriptors: *Cannabidiol; Tetrahydrocannabinol; Cannabinoids; Therapeutic uses; Psychiatry*

Resumo

Objetivo: Revisar os principais avanços no potencial uso terapêutico de alguns compostos canabinoides em psiquiatria. **Método:** Foi realizada busca nos bancos de dado PubMed, SciELO e Lilacs e identificados estudos e revisões da literatura sobre o uso terapêutico dos canabinoides em psiquiatria, em particular canabidiol, rimonabanto, Δ^9-tetraidrocanabinol e seus análogos. **Resultados:** O canabidiol demonstrou apresentar potencial terapêutico como antipsicótico, ansiolítico, antidepressivo e em diversas outras condições. O Δ^9-tetraidrocanabinol e seus análogos demonstraram efeitos ansiolíticos, na dependência de *cannabis*, bem como adjuvantes no tratamento de esquizofrenia, apesar de ainda carecerem de mais estudos. O rimonabanto demonstrou eficácia no tratamento de sintomas subjetivos e fisiológicos da intoxicação pela *cannabis* e como adjuvante no tratamento do tabagismo. Os potenciais efeitos colaterais, de induzir depressão e ansiedade limitaram o uso clínico deste antagonista CB_1. **Conclusão:** Os canabinoides têm demonstrado que podem ter amplo interesse terapêutico em psiquiatria, porém mais estudos controlados são necessários para confirmar estes achados e determinar a segurança destes compostos.

Descritores: Canabidiol; Tetraidrocanabinol; Canabinoides; Usos terapêuticos; Psiquiatria

Introduction

The *Cannabis sativa* plant has been used for medicinal purposes for thousands of years by different peoples and distinct cultures,[1] although today the plant is known to have adverse effects. There is indication that *cannabis* was used in China before the Christian era to treat conditions such as constipation, pain, malaria, expectoration, epilepsy, and tuberculosis, among others.[2] Similarly, it is known that marijuana has long been used to relieve psychiatric symptoms. In India, over 1000 years before Christ, *cannabis* was described as a hypnotic and tranquilizer in the treatment of anxiety, mania, and hysteria.[3] Also, the Assyrians inhaled *cannabis* to alleviate symptoms of depression.[4]

Later, in the beginning of the 20th Century, *cannabis* extracts were sold for the treatment of mental disorders, primarily as sedatives and hypnotics (to treat insomnia, "melancholy", mania, and *delirium tremens*, among others).[4] However, after the 1930s, the medical use of *cannabis* declined, particularly in psychiatry.[1]

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This decline was due to several reasons related to the fact that, by then, the active principles of *cannabis* had not yet been isolated and the extracts varied in potency and composition, resulting in inconsistent and undesirable effects. In addition, new hypnotic and sedative substances were developed, such as chloral hydrate, barbiturates and paraldehyde.[5] Eventually, *cannabis* was considered an illegal substance, which further limited its use in psychiatry.

However, in the 1960s, the group of Professor Raphael Mechoulam,[6] from Israel, identified the chemical structures of the main components of *cannabis*. Its psychotropic component, Δ^9-tetrahydrocannabinol (Δ^9-THC) initially received more attention. Later, it was discovered that this component binds to cannabinoid receptors (CB_1 and CB_2) in the central nervous system. Following this discovery, the endogenous ligands 2-arachidonoylglycerol and anandamide were isolated. The knowledge that the endocannabinoid system is able to modulate several physiological and possibly pathophysiological processes in psychiatric disorders[7] led to renewed interest in the uses of cannabinoids.

This update reviews the main advances in the potential therapeutic use of some cannabinoid compounds in psychiatry. We concentrate particularly on recent findings – both ours and others' – related to the possible applications of cannabidiol (CBD), a non-psychotropic cannabinoid.

Method

The articles selected for this review were identified through a search performed in the PubMed, Scielo, and Lilacs online databases for studies and reviews concerning therapeutic applications of cannabinoids in psychiatry, particularly CBD, rimonabant, Δ^9-THC, and their analogues. In addition, the reference lists of the selected articles and book chapters consulted were also checked for additional material. The review of studies related to CBD included experimental trials and animal testing. Studies that used smoked *cannabis* were excluded, because it is impossible to establish the dose, composition, and ratio of the different cannabinoids thus ingested and because of the wide individual variation within the samples studied. In respect to rimonabant, Δ^9-THC, and their analogues, we included primarily clinical trials and laboratory surveys in humans, as well as case reports. Studies on extracts containing Δ^9-THC and CBD (Cannador®, for oral use, and Sativex®, an oromucosal spray) were not included because it is difficult to establish the effects of each of these cannabinoids separately.

Results

1. Cannabidiol (CBD)

Since the early 1970s, other cannabinoids have been reported to interfere with the effects of Δ^9-THC; particularly CBD, which is present in large amounts in *Cannabis sativa* but is devoid of the typical effects of the plant.[8]

In healthy volunteers, oral CBD (1mg/kg) administered together with a high dose of Δ^9-THC (0.5mg/kg) significantly attenuated the anxiety and psychotic symptoms induced by the latter.[9] It is known that the concomitant administration of CBD at this dose does not alter, through pharmacokinetic interaction, the plasma levels of Δ^9-THC, and thus these results suggest that CBD might have anxiolytic and/or antipsychotic properties.

1) Anxiolytic effects

a) Animal studies

The two initial studies that investigated a possible anxiolytic effect of CBD in rats arrived at conflicting results. Silveira Filho and Tufik, using the conflict test and suppressed food intake by neophobia, found no anxiolytic effects of CBD in doses above 100mg/kg.[10] Moreover, Zuardi and Karniol demonstrated that CBD (10mg/kg) decreased conditioned emotional responses, increased by Δ^9-THC (2mg/kg).[11]

Later, other studies lent support to the hypothesis that CBD has anxiolytic effects in several animal models: i) conflict tests (drinking behavior punished by electrical shocks) in rats deprived of water;[12,13] ii) behavioral and cardiovascular responses in the conditioned fear paradigm (paw shocks) in rats;[14] iii) acute restraint stress test;[15] iv) contextual fear memory extinction;[16] and v) elevated plus maze in mice[17] and rats.[18-20] In these last studies,[19,20] the effect of CBD had an inverted U-shaped curve. Low doses of CBD increased the exploratory activity in the open arms of the maze, a typical effect of anxiolytic drugs, while higher doses resulted in the return to baseline patterns. This result shed light on the absence of response to CBD in the study by Silveira Filho and Tufik, which used doses of over 100mg/kg.[10]

CBD (20mg/kg) also reverted the reduced social interaction induced by low doses of Δ^9-THC in rats.[21] Recently, the chronic use of CBD was shown to produce anxiolytic-like activity in mice.[22]

The anxiolytic properties of CBD do not seem to be mediated by benzodiazepine receptors;[13] however, this cannabinoid interacts with 5HT1A receptors and this interaction seems to be involved in its anxiolytic-like effects.[15,23]

Taken together, the results from animal studies suggest that low doses of CBD might have anxiolytic effects.

b) Human studies

The acute (oral, inhaled or intravenous) and chronic (oral) administration of CBD to healthy subjects and patients with different conditions produced no significant adverse effects.[9,24,25] Therefore, consonant with results from animal studies, CBD was shown to be a safe compound that can be used in humans in a broad dose range.

A possible anxiolytic effect of CBD was initially studied in healthy subjects submitted to simulated public speaking (SPS). In this test, the subject is asked to speak in front of a video camera for several minutes. During the test, the volunteer's subjective anxiety is measured using self-evaluation scales and anxiety-related physiological responses (heart rate, blood pressure, skin conductance) are measured. SPS has the capacity to induce anxiety that is sensitive to anxiogenic and anxiolytic compounds.[26] The effects of CBD (300mg) on the SPS test were compared to those produced by placebo and by the anxiolytic drugs diazepam (10mg) and ipsapirone (5mg) in a double-blind trial. The results showed

that both CBD and the other two anxiolytic substances attenuated the anxiety induced by SPS.[27]

The SPS test has face validity for social anxiety disorder (SAD), since the fear of speaking in public and its physiological concomitants are considered to be essential aspects of this condition. Given the inexistence of earlier research on the anxiolytic effects of CBD on pathological anxiety, we investigated these effects in patients with SAD (n = 24) compared with healthy individuals submitted to the SPS test. Twelve subjects with SAD received CBD (600mg) and another 12 received placebo, whereas an equal number of healthy participants performed the test without receiving any medication. The SAD group that received CBD presented lower levels of anxiety in the anticipatory and performance phases of the test, fewer somatic symptoms, and less negative self-evaluation as compared with the SAD group that received placebo. The SAD group that received CBD did not differ significantly from the healthy control group, contrary to what happened in the SAD group that received placebo.

In a previous trial, we evaluated the effects of CBD on the regional cerebral blood flow (rCBF) in healthy subjects using single-photon emission computed tomography (SPECT).[28] In this double-blind, cross-over trial, subjects received CBD (400mg) or placebo in two experimental sessions one week apart. In each experimental session one hour after receiving CBD or placebo, subjects were injected with the radioactive tracer technetium-99 for the SPECT scan through intravenous catheters on their arms. Subjective anxiety was measured by means of self-evaluation scales applied before the drugs were administered and immediately before the catheter was introduced and the scan was conducted. The whole procedure proved to be anxiogenic, allowing the anxiolytic effects of CBD to appear if existent. The SPECT analysis showed increased activity in the left parahippocampal gyrus and decreased activity in the left amygdala-hippocampus complex, extending to the hypothalamus, and in the left posterior cingulate cortex. This pattern of brain activity induced by CBD is compatible with anxiolytic-like activity.

Later, Fusar-Poli et al. used functional magnetic resonance imaging (fMRI), which allows the acquisition of a greater number of images with better temporal and spatial resolution, to investigate the neural correlates of the anxiolytic-like properties of CBD in 15 healthy subjects.[29] CBD (600mg) was found to modulate patterns of brain activity during the viewing of fearful facial stimuli, attenuating responses in the amygdala and in the anterior and posterior cingulate cortex. This attenuation pattern was directly correlated with a simultaneous effect of CBD in the modulation of electrodermal responses to fearful stimuli. The same authors also demonstrated that CBD exerts its anxiolytic effects by acting on prefrontal subcortical pathways via the amygdala and anterior cingulate cortex.[30]

Recently, we conducted the first study to investigate the neural correlates of the anxiolytic effects of CBD in a clinical trial,[31] using the same dose, protocol, and design of the SPECT study conducted in healthy subjects described above.[28] Compared to placebo, a single oral dose of CBD was capable to decrease subjectively reported anxiety without increasing sedation in untreated patients with SAD. This finding was associated with decreased activity in the parahippocampal gyrus, hippocampus, and left temporal gyrus; and with increased activity in the left posterior cingulate cortex.

These results show that the modulatory properties of CBD on the activation patterns of limbic and paralimbic areas are consistent with the properties of anxiolytic drugs in patients with psychiatric disorders and in healthy subjects.[32,33] Likewise, these findings suggest that CBD may have anxiolytic properties in pathological anxiety.

2) Antipsychotic effects

a) Animal studies

As a first step in the investigation of a possible antipsychotic action of CBD, the effects of the substance were compared with those of haloperidol, a typical antipsychotic, in animal models generally used to investigate the antipsychotic properties of new compounds.[34] Both CBD (15-60mg/kg) and haloperidol (0.25-0.5mg/kg) had a dose-dependent effect of reducing the occurrence of stereotyped behaviors induced by apomorphine, such as repetitive sniffing and biting. Haloperidol had an effect in the catalepsy test (time elapsed with the front paws resting on an elevated bar), which did not occur with CBD, even when high doses were used (480mg/kg). The induction of catalepsy in rodents by the use of antipsychotics is closely related to the tendency of these drugs to provoke Parkinson-like symptoms in patients. A new generation of antipsychotics, the so-called atypical antipsychotics, have a low tendency to provoke Parkinson-like symptoms. In these tests, CBD presented an effect profile that was very similar to that of the standard atypical antipsychotic clozapine.

In another experiment, the effects of CBD on amphetamine- and ketamine-induced hyperactivity in mice were investigated.[35] The effects of CBD were compared to those of haloperidol and clozapine. CBD (15-60mg/kg) inhibited amphetamine-induced hyperactivity in mice in a dose-dependent manner, in agreement with the results obtained with apomorphine,[34] an agonist of dopamine receptors. It was also observed that CBD inhibited ketamine-induced hyperlocomotion, which extends the observation of a typical antipsychotic-like effect of CBD into a model based on glutamate. Both haloperidol and clozapine were capable of inhibiting hyperlocomotion in the two models, as expected. However, CBD and clozapine did not induce catalepsy, but haloperidol did. This strengthens the view that CBD exhibits a profile similar to that of atypical antipsychotic drugs. These results were later supported by a trial that indicated that CBD and clozapine are associated with similar brain activation patterns, inducing *Fos* immunoreactivity in the prefrontal cortex but not in the dorsal striatum, whereas haloperidol was associated with an opposite result in these two brain areas.[36]

b) Human studies

The use of experimental psychopathology models in humans can provide important insights on the therapeutical properties of drugs, preceding clinical trials with patients. One of the models used to evaluate a possible antipsychotic effect of CBD was that

of binocular depth inversion (BDI). In this model, CBD reduced the impairment in the description of illusory images produced by nabilone, a synthetic cannabinoid analogous to Δ^9-THC, suggesting an effect similar to that of antipsychotics in patients with schizophrenia.[37]

Currently, subanesthetic doses of ketamine have been suggested as one of the best experimental models to reproduce psychotic symptoms in healthy individuals, because it acts as an antagonist of NMDA receptors and, at low doses, increases the release of glutamate that can act on non-NMDA receptors. In this model, the drug causes dissociative, positive, negative, and cognitive symptoms similar to those characteristic of schizophrenia.[38] This model of psychotic symptoms induced by ketamine was used to compare the effects of CBD (600mg) and placebo in 10 healthy subjects in a double-blind procedure.[39] Subjects were submitted to two experimental sessions, less than one week apart. Subjects randomly received CBD or placebo in each session. We observed that CBD attenuated the elevations provoked by ketamine in the total scores and factors of a scale used to evaluate dissociative symptoms (Clinician-Administered Dissociative States Scale – CADSS), and that this effect was significant for the depersonalization factor, which reinforces the hypothesis that CBD has an antipsychotic effect. Likewise, this possible effect on dissociative symptoms also raises the hypothesis that CBD may have a therapeutic potential in the treatment of post-traumatic stress disorder, *cannabis* intoxication, and some personality disorders (Table 1).

A recent fMRI trial conducted together with a pharmacological challenge with CBD and Δ^9-THC supported the idea that CBD may have antipsychotic properties.[40] The authors of this study observed that Δ^9-THC and CBD had opposite effects in terms of the activation of brain areas using different tasks. In a second experiment, the pre-treatment with CBD was capable of preventing the acute induction of psychotic symptoms by Δ^9-THC.[40] This result is consistent with the finding that subjects smoking strains of *cannabis* containing CBD in addition to Δ^9-THC are less prone to present psychotic symptoms than subjects smoking strains of *cannabis* without CBD.[41]

Based on these previous studies and considering the evidence related to a possible dysfunction of the cannabinoid system in schizophrenia[42] and its relationship with the typical features of this disorder, we investigated the effects of CDB on selective attention and on the pattern of electrodermal responsiveness to auditory stimuli in patients with schizophrenia.[43] Twenty-eight patients were evaluated with the Stroop Color Word Test (SCWT) in two experimental sessions. In the first session, no drugs were administrated and in the second session the patients were divided into three groups, each receiving a single dose of CBD 300mg, CBD 600mg or placebo. We observed that the acute administration of CBD in a single dose had no beneficial effects on the performance of patients with schizophrenia in the SCWT; however, this is not enough to refute the hypothesis that the continued administration of CBD can result in improved cognitive functioning in schizophrenia.

Table 1 – Possible uses of cannabidiol in psychiatry

Use	Level of evidence
Psychosis	
Schizophrenia	+++
Associated with Parkinson's disease	++
Cannabis-induced	++
Associated with epilepsy	?
High risk for psychosis/prodromal	?
Anxiety	
Healthy	++
Cannabis induced	++
Social anxiety disorder	++
Post-traumatic stress disorder	?
Panic disorder	?
Mood disorders	
Affective disorder (mania)	–
Depression	+
Abstinence syndrome	
Cannabis	++
Heroine	+
Tobacco	?
Other substance	?
Sleep disorders	
Insomnia	++

+++ strong evidence (controlled clinical trials in humans)
++ moderate evidence (acute controlled trials and/or non-controlle trials in humans)
+ some evidence (studies in animals)
– absence of evidence (studies in humans and/or animals)
? treatment rationale

The absence of toxic effects associated with CBD and the pre-clinical evidence from animal and human studies related to its potential anxiolytic and antipsychotic effects made trials ethically acceptable. Initially, trials were open-label and had a restricted number of subjects submitted to treatment with CBD. In 1995, Zuardi et al. published a case report of a 19-year old female diagnosed with schizophrenia and presenting severe side effects after treatment with conventional antipsychotics.[44] After hospitalization, the patient remained four days without medication and was then treated for four weeks with increasing doses of CBD up to 1,500mg/day. After this period, CBD was replaced by placebo for four days, and then haloperidol was introduced at increasing doses up to 12.5mg/day. The symptoms were assessed by the assisting psychiatrist and a blinded-psychiatrist with the Brief Psychiatric Rating Scale (BPRS). The treatment with CBD significantly improved the evaluated symptoms, which had a tendency to worsen when the substance was suspended. Symptoms decreased again with haloperidol, but not beyond the levels reached with CBD. As mentioned before, CBD produced no adverse effects, differently from haloperidol.

More recently, we expanded the use of CBD to three male subjects with 22 and 23 years of age, diagnosed with schizophrenia resistant to the treatment with conventional antipsychotics.[45,46] The patients were hospitalized and received placebo for the first five days, CBD from day 6 to day 35, placebo for another five

days and, finally, olanzapine for at least 15 days. CBD was given at an initial dose of 40mg/day, gradually increased until reaching 1,280mg/day. Patients were assisted by a psychiatrist, responsible for adjusting the doses, and two dose-blinded psychiatrists who applied the BPRS and a scale to screen for adverse effects. Two of the subjects had a mild improvement with CBD and the third did not respond to CBD at all. All the symptoms were exacerbated when the substance was suspended. Only one of the patients improved more with olanzapine than with CBD. The mild improvement presented by one of the patients and the absence of response from the other may be attributable to the fact that these two patients had been considered resistant to antipsychotics, since one of them had only a partial response to clozapine and the other did not respond even to this antipsychotic. None of the patients showed adverse effects with CBD.

A recent four-week exploratory, double-blind, controlled trial, with an adequate number of subjects, confirmed the preliminary results of the antipsychotic properties of CBD described above.[47] In this study, CBD was tested in patients diagnosed with schizophrenia or schizophreniform disorder (DSM-IV) in an acute episode and compared with the antipsychotic amisulpride (an atypical antipsychotic with a mild tendency to produce Parkinson-like side effects). Forty-two patients took part in this trial. In both treatments there was a significant reduction of psychotic symptoms after two to four weeks. No significant differences were observed between the groups; however, CBD induced significantly less side effects, such as extrapyramidal symptoms, increased prolactin levels, and weight gain.

Psychotic symptoms are common in patients with Parkinson's disease (PD)[48] and the management of this condition is considered as a great challenge to clinicians. This is due to several factors: i) decrease in the dose of antiparkinsonian agents usually aggravates motor symptoms; ii) the additional use of conventional antipsychotics may further exacerbate motor signs; and iii) clozapine, the most effective atypical antipsychotic for the treatment of this condition, can have unacceptable side effects, especially neurological and hematological.[49] Therefore, because of the lack of safe and effective pharmaceutical interventions for psychosis in PD and considering the relevance of a possible antipsychotic effect of CBD, we have recently evaluated the efficiency, safety, and tolerability of this cannabinoid in patients with PD and psychosis.[50]

In an open trial, we tested the use of CBD in six out-patients diagnosed with PD and associated psychotic symptoms for at least three months. These patients received a flexible oral dose of CBD (starting at 150mg/day) for four weeks, in addition to their usual treatment. Both psychotic and motor symptoms were significantly reduced and cognitive symptoms were not exacerbated. These preliminary results suggest that CBD can have beneficial effects in the treatment of PD. A double-blind placebo controlled trial is currently underway to evaluate this possibility.

3) Sedative effects and effects on sleep

One of the first effects of CBD to be observed was its sedative action, reported in rats in which the use of this cannabinoid was found to reduce movement and operant behavior.[51,52] Later, sleep-inducing properties and increase in total sleep were described.[53] In a randomized, double-blind trial, volunteers complaining of insomnia and without any other physical or psychiatric conditions received three doses of CBD (40, 80, and 160mg), placebo, and nitrazepam (5mg). The treatments lasted for one week. When compared to placebo, CBD (160mg) significantly increased the number of subjects that slept for seven or more hours.[54] Consistent with this finding, many of the subjects included in the abovementioned CBD trial for patients with PD[50] described improvements in the quality of sleep, which is a common problem associated with PD.[55]

Sedative properties have also been consistently reported in healthy volunteers and SAD patients with the use of high oral doses of CBD (300mg to 600mg).[28,56,57] In a trial conducted with healthy participants in the morning, after at least six hours of sleep, the sleep scores of a self-evaluation analogical scale increased with the use of a single dose of CBD 300mg or 600mg, compared to placebo (Figure 1 – adapted from Zuardi et al.[56]).

Nevertheless, there are reports from animal[58,59] and human[57,59] research studies that indicate that CBD increases wakefulness, probably through an increase in dopamine levels.[58] These apparently paradoxal findings related to the effects of CBD on sleep can be explained by the fact that these effects – just like in anxiety – are biphasic, provoking wakefulness at low doses and sedation at higher doses.[57,59]

4) Antidepressant and mood stabilizing properties

Considering that the anxiolytic properties of CBD can be mediated by the activation of 5-HT_{1A} receptors and that this modulation can induce antidepressant effects, this hypothesis has recently been tested using the forced swim test in mice.[60] Like the standard antidepressant imipramine (30mg/kg), CBD (30mg/kg) decreased the immobility time of mice submitted to the forced swim test. The CBD effects were blocked by previous

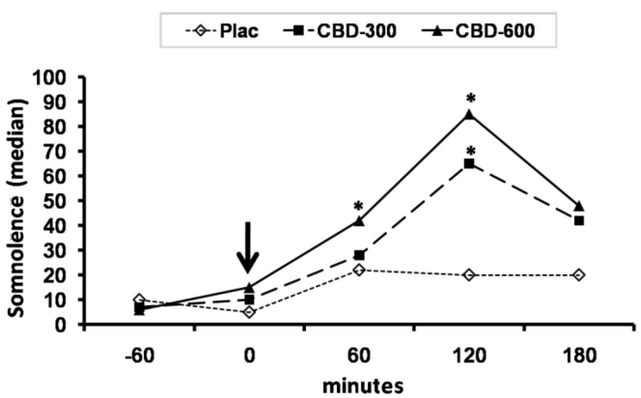

Figure 1 – Median of the "alert – sleepy" scores of the self-reported Visual Analogue Mood Scale in 11 healthy subjects receiving placebo (Plac) or cannabidiol (CBD) in two experimental sessions, in a randomized double-blind trial. (*) indicates statistically significant differences in relation to the baseline assessment (Friedman test; $p < 0.05$).

treatment with a 5-HT_{1A} receptor antagonist, suggesting that the antidepressant-like effect is mediated by the activation of these receptors.

Since CBD was shown to have anticonvulsant,[57,61-63] anxiolytic,[57] antidepressant,[60] and antipsychotic properties similar to those of atypical substances,[46] it was hypothesized that this cannabinoid could have a pharmacological profile similar to that of mood stabilizers.[64] We initially investigated this hypothesis in an animal model of mania using chronic injections of D-amphetamine (D-AMPH) at the dose of 2mg/kg. In this model, CBD was not able to revert or prevent the hyperactivity induced by D-AMPH.Iin addition, CBD increased the levels of brain-derived neurotrophic factor (BDNF) in the reversion experiment.[65]

In parallel with this animal model of mania, we directly investigated the efficiency of CBD in two subjects with bipolar affective disorder (BAD) presenting acute mania episodes.[66] Both subjects received placebo during the first five days of hospitalization and CBD from day 6 to day 30, starting with 600mg/day and reaching 1,200mg per day. The first subject received adjuvant treatment with olanzapine 10-15mg/day, from day 6 to day 20. On day 31, CBD was discontinued and replaced by placebo for another five days. The patient improved only during the period in which CBD was associated with olanzapine, but had no further improvement during monotherapy with CBD. The second subject did not show any improvement in mania symptoms with any dose of CBD during the trial. This finding, together with the negative result of the animal model of mania, suggests that CBD is not effective in the treatment of mania episodes in BAD.

5) *Cannabis* withdrawal syndrome

Among the many symptoms present in the marijuana withdrawal syndrome in chronic users, anxiety and insomnia are the principal manifestations, with onset typically occurring between the second and sixth day after withdrawal. The magnitude and timeline of these effects seem to be comparable to that of tobacco and to the withdrawal syndromes of other substances. This contributes to the development of dependence and difficulty to cessate use.[67]

There are over 160 million *cannabis* users in the world and the amount of people that fulfill the criteria for substance dependence is higher than that of any other illegal substance. However, no currently available pharmacological therapy is considered adequate to treat disorders related to the use of *cannabis.*[68]

Recently, a study in rats showed that CBD inhibits cue-induced heroin seeking and normalizes the associated mesolimbic neuronal disturbances.[69] Based on these findings and on the previously described anxiolytic and sleep properties of CBD, we recently investigated the effects of this cannabinoid in a subject with *cannabis* dependence and a history of *cannabis* withdrawal syndrome.

A 19 year-old female had a history of heavy and continued use of *cannabis* (four to eight cigarettes per day) since 13 years of age. She denied co-use or dependence on any other substance and used almost all her salary to buy marijuana, dedicating much time and effort to obtain the substance. The patient complained of memory, concentration, and attention problems, which interfered with her studies and performance at work. She had tried to stop using the substance at least four times, always presenting, among others, insomnia, anxiety, total loss of appetite, restlessness, migraines, irritability, nightmares, and sudoresis around the forth to sixth day after cessation of use. Resuming the use of the drug resulted in immediate relief of her symptoms.

The subject was hospitalized and received CBD 300mg on the first day, CBD 600mg/day, divided into two doses, from the second to the tenth day, and CBD 300mg on the eleventh day. Serum levels of hepatic enzymes and plasma levels of CBD and Δ^9-THC were monitored daily. Under CBD, the patient did not report any marijuana withdrawal symptom for any of the evaluated items on the Marijuana Withdrawal Symptom Checklist and the Withdrawal Discomfort Score,[70] neither did the subject present the anxiety or dissociative symptoms evaluated by the Hamilton Anxiety Scale (HAS) and the CADSS.

The possible applications of CBD in psychiatry and the currently available evidence in this regard are presented in Table 1.

2. Δ^9-THC and its analogues

Consistent with the previously mentioned reports, one of the most common and controversial hypothesis is that subjects with high levels of anxiety and patients with anxiety disorders use *cannabis* as a form of "self-medication". In support to this view, many subjects report the use of the substance in order to relax and reduce anxiety.[71] This hypothesis was partially based on the results of a double-blind trial with nabilone (3mg/day). In this trial, subjects with anxiety disorders had symptoms reduced after 28 days of treatment.[72] Ilaria et al., in another placebo-controlled crossover trial, also found that nabilone (2-5 mg/day) reduced the symptoms of patients with anxiety disorders.[73]

The same has been said in relation to depression, as certain doses of Δ^9-THC can induce euphoria.[74] In patients with multiple sclerosis, this cannabinoid has been reported to improve mood, probably by reducing painful sensations that are usually accompanied by symptoms of depression.[75] In contrast with these observations, it has been reported that, in subjects exposed to constant doses of marijuana, the substance can provoke an acute and temporary form of induced anxiety, which can resemble a panic attack. This has been consistently described in experimental trials and in several case reports.[76] As in the case of most cannabinoids, these paradoxical findings related to Δ^9-THC could be explained by the fact that its effects on anxiety and mood seem to be dose-dependent, with low and moderate doses showing anxiolytic and euphoric properties and higher doses having anxiogenic properties. In addition, the several cannabinoids (as previously seen with CBD) seem to have distinct individual properties.

A recent trial tested the effects of Δ^9-THC in patients with schizophrenia. Because cannabinoid agonists can exacerbate psychotic symptoms,[77] for ethical reasons the subjects included had a self-reported history of improvement associated with *cannabis* use. Also, these subjects were considered as severe cases resistant to

available treatments (including clozapine), and thus the potential benefits surpassed the risks involved.[78] The authors found that 5mg to 20mg/day (over three to eight weeks) of oral dronabinol (synthetic Δ^9-THC), associated with the antipsychotics being used by the subjects led to significant improvement of schizophrenic symptoms in four out of the six subjects. The improvement in three of these subjects was considered by the authors as resulting from the reduction of psychotic symptoms, and not from an unspecific calming effect. The results suggest that CB_1 agonists can have opposing effects on the psychotic symptoms of patients with schizophrenia. This also seems to be true for anxiety, depression, and other conditions.[76] These effects can be dependent on the cannabinoid dose and on genetic and individual factors that are not currently understood.

The pharmacological therapy for substance dependence can help the treatment in several ways.[67] One approach is to identify substances that can attenuate withdrawal symptoms, such as agonist/substitute substances (nicotine patches for tobacco dependence and methadone for opiate dependence). Accordingly, dronabinol was tested in *cannabis* dependence. Hart et al.,[79] comparing placebo and dronabinol at the doses of 10mg and 20mg given four times per day, discovered that dronabinol reduced some of the subjective effects of *cannabis* in heavy users, though having no impact on self-administration, probably due to problems with the trial design and composition of the studied strain.[80] In a later study, Haney et al.[81] compared dronabinol (10mg, five times per day) and placebo in heavy *cannabis* users with a history of *cannabis* withdrawal symptoms. The authors discovered that dronabinol was effective in reducing withdrawal symptoms and had no subjective effects. Later studies confirmed these findings using low (10mg, three times per day) and high (30mg, three times per day) doses in patients seeking for *cannabis* dependence treatment.[80] Other studies have also extended and confirmed these findings.[67]

Δ^9-THC has also been proposed to act as an hypnotic[82] and recently its analogue nabilone (0.5mg and 1mg), administered to patients with fibromyalgia before going to bed, effectively improved sleep quality as assessed through self-evaluation scales.[83]

Although some patients reported that *cannabis* relieves symptoms of mania and/or depression,[84] attention deficit disorder, and obsessive compulsive disorder, controlled clinical trials with Δ^9-THC and its analogues have not yet been conducted.

3. Rimonabant (SR141716)

Rimonabant (Sanofi-Aventis®), an inverse agonist of the cannabinoid receptor CB_1, was sold in several countries as a substance for treating obesity. Its use induced severe adverse effects, especially anxiety and depression, with cases of suicide induced by the substance. As a result, rimonabant was completely removed from the market and all the clinical trials were interrupted.[85] However, before being removed, the substance was tested in some psychiatric conditions with promising results.

It is currently known that there are few pharmacological options to treat the physiological and psychological effects related to the acute intoxication by *cannabis*.[65] Increasing doses of rimonabant (1, 3, 10, 30, 90mg) were tested in three trials conducted by Huestis et al.[86-88] The substance, administered two hours before smoking an active cigarette (2.64% THC), reduced the physiological and subjective psychological effects of intoxication in a dose-dependent manner. This effect was independent of pharmacokinetic interactions, suggesting a specific property of the compound. Therefore, although rimonabant was used as pre-treatment in these trials, it is possible that substances that block CB_1 receptors can be used to control the physiological and subjective symptoms usually observed in the intoxication by *cannabis*.

Experiments in animals have shown that CB_1 receptor antagonists can reduce the reward/reinforcing properties of many drugs of abuse, including heroin,[89] cocaine,[90] alcohol,[91] and nicotine.[92] Considering these pre-clinical trials and that the success rate of smoking cessation can be increased when weight gain is controlled, rimonabant (20mg/day) was associated with nicotine patches to test its efficacy in smoking cessation.[93] The association increased smoking cessation rates as compared to rimonabant alone. Both groups gained little weight and had low rates of treatment interruption due to adverse psychiatric effects. However, the study design was greatly criticized because it did not provide for definitive conclusions on the efficiency of rimonabant in smoking cessation.[94]

Considering the evidence from previous animal experiments[95] and the "cannabinoid hypothesis of shizophrenia",[42] which proposes the possibility of a hyperactivity of the endocannabinoid system in this condition, a double-blind controlled trial tested rimonabant in schizophrenia.[96] After an interruption period of two to ten days, subjects received 20mg/day of rimonabant, haloperidol (10mg/day) or other experimental drugs for a period of six weeks. Contrary to expectations, rimonabant did not improve symptoms. This can be attributed to the dose, to insufficient administration time, or even to the absence of clinical activity associated with this mechanism of action.

Conclusion

The data presented in this review show that cannabinoids may, in the future, become an important option in the treatment of psychiatric symptoms and disorders. Due to the absence of psychoactive or cognitive effects, to its safety and tolerability, to the existence of clinical trials with positive results, and to its broad pharmacological spectrum, CBD is possibly the cannabinoid more likely to have initial findings translated into clinical practice. In particular, the results indicating that CBD has antipsychotic and anxiolytic properties seem to be well established. However, long-term, double-blind, placebo-controlled trials with samples of subjects with different psychotic and anxiety disorders are still necessary and opportune. Likewise, because CBD effects are biphasic, the determination of adequate treatment ranges for each disorder remains a challenge. Further research to determine the precise mechanisms of action of CBD in the different neuropsychiatric disorders is desirable.

The findings indicating that rimonabant reduces the subjective and physiological effects of acute *cannabis* intoxication show that rimonabant may be a good treatment option for this condition, which is not uncommon in psychiatric emergency services. In addition, results support the role of CB_1 receptors in the mediation of the effects of *cannabis*, which is consistent with previous reports from animal research. However, the important adverse effect of inducing depression[83] has led to the abandonment of rimonabant and interrupted the investigation of its potential use in smoking cessation strategies and in other conditions.Δ^9-THC and its analogues have long been reported to have sedative and hypnotic properties in several conditions, such as multiple sclerosis. One of the most promising uses of these compounds seems to be in the treatment of *cannabis*[67,97] withdrawal. Although Δ^9-THC and its analogues have been described as having beneficial effects on psychotic and mood symptoms,[98] it seems wise to discourage the use of these cannabinoids in these conditions. In addition to the psychotropic effects, the possibility of exacerbating symptoms, the potential for dependence, the presentation of biphasic (different dose-dependent effects) and bidirectional (acute opposing effects in different individuals) properties, regardless of the disorder, hamper the therapeutic application of these cannabinoids. An alternative to this is the careful exploration of the beneficial effects of the association of Δ^9-THC and CBD, which is already used in some neurological disorders. Similarly, other less studied phytocannabinoids [cannabigerol (CBG), cannabichromene (CBC), delta-9-tetrahydrocannabivarin (Δ^9-THCV), cannabidivarin (CBDV), tetrahydrocannabinolic acid (Δ^9-THCA), and cannabidiolic acid (CBDA)] can be of interest to investigators.[59]

In conclusion, it can be stated that the cannabinoid system is a promising target for novel therapeutic interventions in psychiatry.[99] Cannabinoids may be greatly useful in this field; however, additional controlled trials are still required to confirm these findings and determine the safety of these compounds.

Disclosures

Writing group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Antonio Waldo Zuardi	FMRP-USP	CNPq FAPESP	-	-	-	-	THC-Pharm
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** Modest*
*** Significant*
**** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: FMRP-USP = Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo.
For more information, see Instructions for authors.

References

1. Zuardi AW. History of cannabis as a medicine: a review. *Rev Bras Psiquiatr*. 2006;28(2):153-7.
2. Adams R, Hunt M, Clark JH. Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. *J Am Chem Soc*. 1940;62:196-200.
3. Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. *Science.* 1970;169(945):611-2.
4. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale forcombining tetrahydrocannabinol and cannabidiol. *Med Hypotheses.* 2006;66(2):234-46.
5. Martin BR, Mechoulam R, Razdan RK. Discovery and characterization of endogenous cannabinoids. *Life Sci*. 1999; 65(6-7):573-95.
6. Mechoulam R. Endocannabinoids and psychiatric disorders – the road ahead. *Rev Bras Psiquiatr.* 2010;32(Suppl I):S5-6.
7. Leweke FM, Koethe D. Cannabis and psychiatric disorders: it is not only addiction. *Addict Biol.* 2008;13(2):264-75.
8. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol.* 1974;28(1):172-7.
9. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by Δ^9-THC in normal subjects. *Psychopharmacology* (Berl). 1982;76(3):245-50.
10. Silveira Filho NG, Tufik S. Comparative effects between cannabidiol and diazepam on neophobia, food intake and conflict behavior. *Res Commun Psychol Psychiatry Behav*. 1981;6:25-6.
11. Zuardi AW, Karniol IG. Changes in the conditioned emotional response of rats induced by Δ9-THC, CBD and mixture of the two cannabinoids. *Arq Biol Tecnol.* 1983;26:391-7.
12. Musty RE, Conti LH, Mechoulam R. Anxiolytic properties of cannabidiol. In: Harvey DJ, editor. *Marihuana '84. Proceedings of the Oxford Symposium on Cannabis*. Oxford: IRL Press Limited; 1984. p.713-9.
13. Moreira FA, Aguiar DC, Guimarães FS. Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(8):1466-71.
14. Resstel LB, Joca SR, Moreira FA, Corrêa FM, Guimarães FS. Effects of cannabidiol and diazepam on behavioral and cardiovascular responses induced by contextual conditioned fear in rats. *Behav Brain Res*. 2006;172(2):294-8.

15. Resstel LB, Tavares RF, Lisboa SF, Joca SR, Corrêa FM, Guimarães FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol*. 2009;156(1):181-8.

16. Bitencourt RM, Pamplona FA, Takahashi RN. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. *Eur Neuropsychopharmacol*. 2008;18(12):849-59.

17. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. *J Pharmacol Exp Ther*. 1990;253(3):1002-9.

18. Campos AC, Guimarães FS. Evidence for a potential role for TRPV1 receptors in the dorsolateral periaqueductal gray in the attenuation of the anxiolytic effects of cannabinoids. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(8):1517-21.

19. Moreira FA, Campos AC, Guimarães FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology* (Berl). 2008;199(2):223-30.

20. Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology* (Berl). 1990;100(4):558-9.

21. Malone DT, Jongejan D, Taylor DA. Cannabidiol reverses the reduction in social interaction produced by low dose Delta(9)-tetrahydrocannabinol in rats. *Pharmacol Biochem Behav*. 2009;93(2):91-6.

22. Long LE, Chesworth R, Huang XF, McGregor IS, Arnold JC, Karl T. A behavioural comparison of acute and chronic Delta9tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. *Int J Neuropsychopharmacol*. 2009;29:1-16.

23. Campos AC, Guimarães FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology* (Berl). 2008;199(2):223-30.

24. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology*. 1980;21(3):175-85.

25. Consroe P, Laguna J, Allender J, Snider S Ster L, Sandyr R, Kennedy K, Schram K. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav.* 1991;40(3):701-8.

26. Hallak JE, Crippa JA, Quevedo J, Roesler R, Schröder N, Nardi AE, Kapczinski F. National Science and Technology Institute for Translational Medicine (INCT-TM): advancing the field of translational medicine and mental health. *Rev Bras Psiquiatr.* 2010;32(1):85-90.

27. Zuardi AW, Cosme RA, Graeff FG, Guimarães FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. *J Psychopharmacology.* 1993;7:82-8.

28. Crippa JA, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JE, McGuire PK, Filho Busatto G. Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*. 2004;29(2):417-26.

29. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry*. 2009;66(1):95-105.

30. Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, Martin-Santos R, Seal ML, O'Carrol C, Atakan Z, Zuardi AW, McGuire P. Modulation of effective connectivity during emotional processing by Delta9-tetrahydrocannabinol and cannabidiol. *Int J Neuropsychopharmacol*. 2009;24:1-12.

31. Crippa JA, Derenusson G, Zuardi AW, Wichert-Ana L, Duran F, Ferrari TB, Martin-Santos R, McGuire PK, Busatto GF, Hallak JE. The effect of cannabidiol (CBD), a cannabis sativa constituent, on neural correlates of anxiety: a regional cerebral blood flow study. *Schizophrenia Bulletin*; 12th International Congress on Schizophrenia Research; San Diego, Mar 28-Apr 01, 2009;35(Suppl 1):197-198.

32. Trzesniak C, Araújo D, Crippa JA. Magnetic resonance spectroscopy in anxiety disorders. *Acta Neuropsychiatrica.* 2008;20(2):56-71.

33. Ferrari MC, Busatto GF, McGuire PK, Crippa JA. Structural magnetic resonance imaging in anxiety disorders: an update of research findings. *Rev Bras Psiquiatr*. 2008;30(3):251-64.

34. Zuardi AW, Rodrigues JA, Cunha JM. Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacology* (Berl). 1991;104(2):260-4.

35. Moreira FA, Guimarães FS. Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. *Eur J Pharmacol*. 2005;512(2-3):199-205.

36. Guimarães VM, Zuardi AW, Del Bel EA, Guimarães FS. Cannabidiol increases Fos expression in the nucleus accumbens but not in the dorsal striatum. *Life Sci*. 2004;75(5):633-8.

37. Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich M. Different effec os cannabinoids: relevance to psychosis and schizophrenia. *Rev Bras Psiquiatr.* 2010;32(Suppl I):S15-30.

38. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;51(3):199-214.

39. Bosi DC, Hallak JE, Dursun SM, Deakin JF, Zuardi AW. Effects of cannabidiol on (s)-ketamine-induced psychopathology in healthy volunteers. *J Psychopharmacology.* 2003;17:A55.

40. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O' Carroll CM, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology.* 2010;35(3):764-74.

41. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenialike symptoms in people who use cannabis. *Br J Psychiatry.* 2008;192(4):306-7.

42. Müller-Vahl KR, Emrich HM. Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. *Expert Rev Neurother*. 2008;8(7):1037-48.

43. Hallak JE, Machado-de-Sousa JP, Crippa JA, Sanches RF, Trzesniak C, Chaves C, Bernardo SA, Regalo SC, Zuardi AW. Performance of schizophrenic patients in the Stroop Color Word Test and electrodermal responsiveness after acute administration of cannabidiol (CBD). *Rev Bras Psiquiatr.* 2010;32(1):56-61.

44. Zuardi AW, Morais SL, Guimarães FS, Mechoulam R. Anti-psychotic effect of cannabidiol. *J Clin Psychiatry.*1995;56(10):485-6.

45. Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE, Crippa JA. Cannabidiol monotherapy for treatment-resistant schizophrenia. *J Psychopharmacol*. 2006;20(5):683-6.

46. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res.* 2006;39(4):421-9.

47. Leweke FM, Koethe D, Gerth CW, Nolden BM, Schreiber D, Hänsel A, Neatby MA, Juelicher A, Hellmich M, Klosterkötter J. Cannabidiol as an antipsychotic. A double-blind, controlled clinical trial on cannabidiol vs. amisulpride in acute schizophrenia. *Eur Psychiatry.* 2007;22:S14.02

48. Naimark D, Jackson E, Rockwell E, Jeste DV. Psychotic symptoms in Parkinson's disease patients with dementia. *J Am Geriatr Soc*. 1996;44(3):296-9.

49. Thanvi BR, Lo TC, Harsh DP. Psychosis in Parkinson's disease. *Postgrad Med J.* 2005;81(960):644-6.

50. Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, Dursun SM, Tumas V. Cannabidiol for the treatment of psychosis in Parkinson's disease. *J Psychopharmacol.* 2009;23(8):979-83.

51. Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia.* 1973;33(1):53-70.

52. Davis WM, Borgen LA. Effects of cannabidiol and delta-9-tetrahydrocannabinol on operant behavior. *Res Commun Chem Pathol Pharmacol.* 1974;9(3): 453-62.

53. Monti JM. Hypnoticlike effects of cannabidiol in the rat. *Psychopharmacology* (Berl). 1977;55(3):263-5.

54. Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol.* 1981;21(8-9 Suppl):417S-27S.

55. Chagas MH, Tumas V, Loureiro SR, Hallak JE, Trzesniak C, de Sousa JP, Rodrigues GG, Santos Filho A, Crippa JA. Validity of a Brazilian version of the Zung self-rating depression scale for screening of depression in patients with Parkinson's disease. *Parkinsonism Relat Disord.* 2010;16(1):42-5.

56. Zuardi AW, Guimarães 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.

57. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr*. 2008;30(3):271-80.

58. Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colín R. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. *FEBS Lett.* 2006;580(18):4337-45.

59. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci.* 2009;30(10):515-27.

60. Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol.* 2010;159(1):122-8.

61. Carlini EA, Leite JR, Tanhauser M, Berardi AC. Cannabidiol and cannabis sativa extract protect mice and rats against convulsive agents. *J Pharm Pharmacol.* 1973;25(8):664-5.

62. Izquierdo I, Orsingher OA, Berardi AC. Effect of cannabidiol and other Cannabis sativa compounds on hippocampal seizures discharges. *Psychopharmacologia*. 1973;28(1):95-102.

63. Turkanis SA, Cely W, Olsen DM, Karler R. Anticonvulsant properties of cannabidiol. *Res Communic Chem Pathol Pharmacol*. 1974;8(2):231-46.

64. Ashton CH, Moore PB, Gallagher P, Young AH. Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. *J Psychopharmacol.* 2005;19(3):293-300.

65. Valvassori SS, Elias G, de Souza B, Petronilho F, Dal-Pizzol F, Kapczinski F, Trzesniak C, Tumas V, Dursun S, Chagas MH, Hallak JE, Zuardi AW, Quevedo J, Crippa JA. Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania. *J Psychopharmacol*. In press 2009.

66. Zuardi A, Crippa J, Dursun S, Morais S, Vilela J, Sanches R, Hallak J. Cannabidiol was ineffective for manic episode of bipolar affective disorder. *J Psychopharmacol.* 2010;24(1):135-7.

67. Budney AJ, Vandrey RG, Stanger C. Pharmacological and Psychosocial Interventions for Cannabis Use Disorders. *Rev Bras Psiquiatr.* In press 2010.

68. Vandrey R, Haney M. Pharmacotherapy for cannabis dependence: how close are we? *CNS Drugs.* 2009;23(7):543-53.

69. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *J Neurosci.* 2009; 29(47):14764-9.

70. Budney AJ, Hughes JR, Moore BA, Novy PL. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Arch Gen Psychiatry*. 2001;58(10):917-24.

71. Boys A, Marsden J, Griffiths P, Fountain J, Stillwell G, Strang J. Substance use among young people: the relationship between perceived functions and intentions. *Addiction.* 1999;94(7):1043-50.

72. Fabre LF, McLendon D. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. *J Clin Pharmacol*. 1981;21(8-9 Suppl):377S-382S.

73. Ilaria RL, Thornby JI, Fann WE. Nabilone, a cannabinol derivative, in the treatment of anxiety neurosis. *Curr Ther Res*. 1981;29:943-9.

74. Ilan AB, Gevins A, Coleman M, Elsohly MA, de Wit H. Neurophysiological and subjective profile of marihuana with varying concentrations of cannabinoids. *Behav Pharmacol.* 2005;16(5-6):487-96.

75. Svendson KB, Troels SJ, Fleming WB. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomized double blind placebo controlled crossover trial. *BMJ*. 2004;329(7460): 253-7.

76. Crippa JA, Zuardi AW, Martín-Santos R, Bhattacharyya S, Atakan Z, McGuire P, Fusar-Poli P. Cannabis and anxiety: a critical review of the evidence. *Hum Psychopharmacol*. 2009;24(7):515-23.

77. Sewell RA, Skosnik PD, Garcia-Sosa I, Ranganathan M, D'Souza DC. Behavioral cognitive and psychophysiological effects os cannabinoids: relevance to psychosis and schizophrenia. *Rev Bras Psiquiatr.* 2010;32(Suppl I):S15-30.

78. Schwarcz G, Karajgi B, McCarthy R. Synthetic delta-9-tetrahydrocannabinol (dronabinol) can improve the symptoms of schizophrenia. *J Clin Psychopharmacol.* 2009;29(3):255-8.

79. Hart CL, Haney M, Ward AS, Fischman MW, Foltin RW. Effects of oral THC maintenance on smoked marijuana self-administration. *Drug Alcohol Depend*. 2002;67(3):301-9.

80. Levin FR, Kleber HD. Use of dronabinol for cannabis dependence: two case reports and review. *Am J Addict*. 2008;17(2):161-4.

81. Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Foltin RW. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology*. 2004;29(1):158-70.

82. Cousens K, DiMascio A. (-) Delta 9 THC as an hypnotic. An experimental study of three dose levels. *Psychopharmacologia.* 1973;33(4):355-64.

83. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg.* 2010;110(2):604-10.

84. Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs.* 1998;30(2):171-7.

85. Moreira FA, Crippa JA. The psychiatric side-effects of rimonabant. *Rev Bras Psiquiatr.* 2009;31(2):145-53.

86. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET,Frank RA. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Arch Gen Psychiatry*. 2001;58(4):322-8.

87. Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, Huestis MA. The cannabinoid CB1 receptor antagonist rimonabant attenuates the hypotensive effect of smoked marijuana in male smokers. *Am Heart J*. 2006;151(3):754.e1-754.e5.

88. Huestis MA, Boyd SJ, Heishman SJ, Preston KL, Bonnet D, Le Fur G, Gorelick DA. Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. *Psychopharmacology* (Berl). 2007;194(4):505-15.

89. Navarro M, Carrera MR, Fratta W, Valverde O, Cossu G, Fattore L, Chowen JA, Gomez R, del Arco I, Villanua MA, Maldonado R, Koob GF, Rodriguez de Fonseca F. Functional interaction between opioid and cannabinoid receptors in drug self-administration. *J Neurosci*. 2001;21(14):5344-50.

90. De Vries TJ, Shaham Y, Homberg JR, Crombag H, Schuurman K, Dieben J, Vanderschuren LJ, Schoffelmeer AN. A cannabinoid mechanism in relapse to cocaine seeking. *Nat Med*. 2001;7(10):1151-4.

91. Colombo G, Vacca G, Serra S, Carai MA, Gessa GL. Suppressing effect of the cannabinoid CB1 receptor antagonist, SR 141716, on alcohol's motivational properties in alcohol-preferring rats. *Eur J Pharmacol*. 2004;498(1-3):119-23.

92. Cohen C, Perrault G, Voltz C, Steinberg R, Soubrié P. SR141716, a central cannabinoid (CB(1)) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. *Behav Pharmacol.* 2002;13(5-6):451-63.

93. Rigotti NA, Gonzales D, Dale LC, Lawrence D, Chang Y; CIRRUS Study Group. A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. *Addiction*. 2009;104(2):266-76.

94. Stapleton JA. Trial comes too late as psychiatric side effects end hope for rimonabant. *Addiction*. 2009;104(2):277-8.

95. Poncelet M, Barnouin MC, Brelière JC, Le Fur G, Soubrié P. Blockade of cannabinoid (CB1) receptors by 141716 selectively antagonizes drug-induced reinstatement of exploratory behaviour in gerbils. *Psychopharmacology* (Berl). 1999;144(2):144-50.

96. Meltzer HY, Arvanitis L, Bauer D, Rein W; Meta-Trial Study Group. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *Am J Psychiatry*. 2004;161(6):975-84.

97. Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007;86(1):22-9.

98. Gruber AJ, Pope HG, Brown ME. Do patients use marijuana as an antidepressant? *Depression.* 1996;4:77-80.

99. Bhattacharyya S, Crippa JA, Martin-Santos R, Winton-Brown T, Fusar-Poli P. Imaging the neural effects of cannabinoids: current status and future opportunities for psychopharmacology. *Curr Pharm Des*. 2009;15(22):2603-14.