

# Accepted Manuscript

Could cannabidiol be used as an alternative to antipsychotics?

Marc Fakhoury

PII: S0022-3956(16)30104-2

DOI: [10.1016/j.jpsychires.2016.05.013](https://doi.org/10.1016/j.jpsychires.2016.05.013)

Reference: PIAT 2871

To appear in: *Journal of Psychiatric Research*

Received Date: 4 March 2016

Revised Date: 27 April 2016

Accepted Date: 26 May 2016

Please cite this article as: Fakhoury M, Could cannabidiol be used as an alternative to antipsychotics?, *Journal of Psychiatric Research* (2016), doi: 10.1016/j.jpsychires.2016.05.013.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**Could cannabidiol be used as an alternative to antipsychotics?**

Marc Fakhoury

Department of Neurosciences, Faculty of Medicine, Université de Montréal, Montreal, Quebec,  
Canada

Corresponding Author: Marc Fakhoury

Address: Department of Neurosciences, University of Montreal, Montreal, QC, Canada H3C 3J7.

Tel.: +1 514.710.7060;

E-mail: [marc.fakhoury@umontreal.ca](mailto:marc.fakhoury@umontreal.ca)

**Abstract**

Schizophrenia is a mental disorder that affects close to 1% of the population. Individuals with this disorder often present signs such as hallucination, anxiety, reduced attention, and social withdrawal. Although antipsychotic drugs remain the cornerstone of schizophrenia treatment, they are associated with severe side effects. Recently, the endocannabinoid system (ECS) has emerged as a potential therapeutic target for pharmacotherapy that is involved in a wide range of disorders, including schizophrenia. Since its discovery, a lot of effort has been devoted to the study of compounds that can modulate its activity for therapeutic purposes. Among them, cannabidiol (CBD), a non-psychoactive component of cannabis, shows great promise for the treatment of psychosis, and is associated with fewer extrapyramidal side effects than conventional antipsychotic drugs. The overarching goal of this review is to provide current available knowledge on the roles of the dopamine system and the ECS in schizophrenia, and to discuss key findings from animal studies and clinical trials investigating the antipsychotic potential of CBD.

**Keywords:** antipsychotics; cannabidiol; endocannabinoid system; psychosis; schizophrenia

## 1. Introduction

Schizophrenia is a complex mental health disorder that poses serious complications to the individual and to the society in terms of health care costs. This disease typically leads to low quality of life, long term disability, and reduced ability to work (Makinen et al., 2008). The median lifetime prevalence and incidence of schizophrenia are estimated at 0.72% and 15.2 per 100 000 individuals a year respectively (McGrath et al., 2008). However, the relative risk of this disease varies greatly across different locations and ethnicity, and has been shown to be particularly elevated among migrant group (Bhugra, 2004; Bhugra and Becker, 2005). Symptoms of schizophrenia usually emerge during adolescence and early adulthood, and are clustered into three main categories; negative, positive, and cognitive. Negative symptoms, which are some of the most difficult to diagnose, refer to reduced emotional and behavioral response (Patel et al., 2014). Among them, blunted affect and anhedonia are the most strongly manifested in schizophrenic patients, but other symptoms such as reduced motivation and social interaction are also commonly observed (Makinen et al., 2008). In contrast to negative symptoms, positive symptoms are generally more easily identified. They are characterized by hallucinations, delusion, disorganized thinking and movement disturbances (Patel et al., 2014). Finally, cognitive deficits in schizophrenia include reduced episodic memory, poor executive functioning, low processing speed and disorganized speech, ultimately impairing the ability of the individual to properly think and communicate (Patel et al., 2014; Sheffield et al., 2014).

One of the most studied and recognized model of schizophrenia is the dopamine hypothesis (Howes and Kapur, 2009). This model attributes the symptoms of the disease to a hyperfunction of dopaminergic signaling in the mesolimbic system. It draws evidence from the observation that a large number of antipsychotics have the ability to block dopamine D2 receptors (Seeman and Lee, 1975; Howes and Kapur, 2009). Antipsychotics are divided into two classes: the typical (or first generation) and the atypical (or second generation). Although being efficient in managing some symptoms of schizophrenia, treatment with typical antipsychotics usually results in extrapyramidal side effects such as spasticity and tardive dyskinesia (Tandon and Jibson, 2002), whereas treatment with atypical antipsychotics leads to severe complications including weight gain, sedation and hyperlipidemia (Ucok and Gaebel, 2008).

Besides the dopamine hypothesis, evidence also support the notion that a dysregulation of the endocannabinoid system (ECS) may be linked to the pathophysiology of schizophrenia. The ECS is a signalling system that is mainly composed of the cannabinoid receptors types 1 (CB<sub>1</sub>) and type 2 (CB<sub>2</sub>), the endogeneous ligands *N*-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), as well as the hydrolytic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (Parsons and Hurd, 2015). Evidence supporting the role of the ECS in schizophrenia comes in part from post-mortem, imaging, and neurochemical studies showing abnormal brain levels of cannabinoid receptors and endocannabinoid ligands during the course of schizophrenia (Vigano et al., 2009; Dalton et al., 2011; Muguruza et al., 2013). Namely, some studies have shown that patients with schizophrenia-like symptoms have increased endocannabinoid signaling as a result of higher cannabinoid receptor density in certain brain areas (Dalton et al., 2011; Jenko et al., 2012). In addition, chronic administration of delta-9-tetrahydrocannabinol (THC), which acts as an agonist to cannabinoid receptor, was shown to precipitate the occurrence of schizophrenia-like symptoms in healthy subjects (D'Souza et al., 2004), and exacerbate the core psychotic and cognitive deficits in antipsychotic-treated schizophrenic patients (D'Souza et al., 2005). These findings led to the formulation of the "cannabinoid hypothesis of schizophrenia", which

speculates that a hyperactivity of the ECS may contribute to the development of schizophrenia-like symptoms. As such, the use of compounds that modulate its activity could have a tremendous potential for therapeutic interventions. One such compound is cannabidiol (CBD), a non-psychoactive component of cannabis. CBD was recently suggested as a promising antipsychotic agent because of its ability to prevent the actions of THC, the main constituent of cannabis (Niesink and van Laar, 2013). However, despite recent advances in research, the antipsychotic effects of CBD are not fully understood, and there are still debates as to whether this compound should be used as a treatment for schizophrenic patients.

The aim of this review is to provide a better understanding of the current treatment approaches used for schizophrenia, and to discuss whether CBD could be used as an effective line of treatment for this debilitating disease. This review first starts by describing evidences supporting a role for dopamine and endocannabinoids in schizophrenia, and provides an overview of the most commonly encountered side effects associated with currently used antipsychotics. This paper also draws on findings of animal studies and clinical trials exploring the therapeutic profile of CBD in schizophrenia, and discusses whether this compound could be used as an alternative to antipsychotics.

## **2. Dopamine in schizophrenia**

The two dopaminergic pathways that are implicated in the onset of schizophrenia-like symptoms are the mesolimbic and mesocortical pathways. The mesolimbic pathway is comprised of dopaminergic projections that originate from the ventral tegmental area (VTA), and that innervate regions of the brain like the nucleus accumbens (NAc), which plays a key role in regulating the positive symptoms of schizophrenia. On the other hand, the mesocortical dopaminergic pathway is involved in emotional and cognitive responses, and is composed of dopaminergic neurons that project from the VTA to the prefrontal cortex (PFC). Excessive subcortical release of dopamine causes positive symptoms by augmenting D2 dopamine receptor function, whereas reduced dopamine activity in the PFC causes negative symptoms and cognitive impairment mainly as a result of decreased D1 dopamine receptor function (Lieberman, 2004; Brisch et al., 2014).

Most of the evidence supporting the role of dopamine in schizophrenia comes from studies employing animal models. Social isolation rearing in rats, which is regarded as a neurodevelopmental model of schizophrenia, leads to reduced and increased level of dopamine in the PFC and striatum respectively (Moller et al., 2013). Similarly, rats treated with phencyclidine (PCP), a pharmacological model of schizophrenia, display increased striatal dopamine release following an amphetamine challenge (Balla et al., 2001). Increased level of dopamine in the brain was shown to correlate with profound behavioral changes reminiscent of schizophrenia, including deficits in sensorimotor gating (Kwek and van den Buuse, 2013).

Of further relevance, dopamine interact with a wide variety of neurotransmitters in the brain that are also involved in schizophrenia. For instance, neurotransmitter pathways such as those of glutamate and gamma-aminobutyric acid (GABA) appear to have a significant influence on the regulation of dopamine level in the brain (Brisch et al., 2014). Both preclinical and clinical data have supported the notion that reduced glutamate receptor functioning may represent a predominant cause for dopamine dysfunction in schizophrenia (Kegeles et al., 2000; Balla et al., 2001). The existence of regulatory feedback loops between serotonin and dopaminergic neurotransmitters is also relevant to the pathophysiology of schizophrenia, and has been

described in details in previous papers (Bhattacharyya et al., 2006; Alex and Pehek, 2007; Di Pietro and Seamans, 2007; Remington, 2008).

### 3. Typical and atypical antipsychotics: the end of an era?

Typical and atypical antipsychotics are currently the two main types of medication used for the treatment of schizophrenia. They both have a successful track record in treating hallucinations, paranoia, and other symptoms of schizophrenia. Atypical antipsychotics are currently considered a better option than conventional drugs because they are less prone to induce secondary motor effects, and are associated with overall improved subjective experience and compliance to treatment regimen (Lambert et al., 2011; Ginovart and Kapur, 2012). However, despite the additional benefits of the second generation antipsychotics, approximately half of patients with schizophrenia are non-adherent to pharmacological treatment (Caspi et al., 2004; Morken et al., 2008).

Chlorpromazine, the first typical antipsychotic drug, was discovered serendipitously in the early 1950s, and was soon found to produce extrapyramidal side effects reminiscent of Parkinson's disease (Miller, 2009). The concomitant presence of antipsychotic and motor effects led to this group of drugs being called "neuroleptic drugs" (Miller, 2009). Their therapeutic efficiency is explained by their ability to reduce dopaminergic transmission in the brain through blockade of dopamine D<sub>2</sub> receptors. After the advent of chlorpromazine, other typical antipsychotics including haloperidol, trifluoperazine, thioridazine and fluphenazine were introduced, but were all found to exhibit serious side-effects when administered to schizophrenic patients (Ramachandiraiah et al., 2009). In particular, motor effects such as tremors, spasticity, akathisia and tardive dyskinesia were very commonly observed, and were mainly due to striatal dopamine reduction in the brain following antipsychotic treatment (Mathews et al., 2005; Dold et al., 2015). Long term use of typical antipsychotics also leads to dopamine supersensitivity as a result of increased level of D<sub>2</sub> receptors in a high affinity state (D<sub>2</sub><sup>high</sup>) (Seeman et al., 2005; Seeman, 2011). At the clinical level, antipsychotic-induced dopamine supersensitivity is associated with worsened positive symptoms, making schizophrenic patients less compliant with their treatment regimen.

Several years following the introduction of typical antipsychotics, Clozapine, the first atypical antipsychotic drug, was discovered and released into the European market. In contrast to typical antipsychotics, this type of drug is associated with lower risk of extrapyramidal side effects due to its low binding affinity to dopamine D<sub>2</sub> receptors (Kapur and Seeman, 2001). Atypical antipsychotics like clozapine also exhibit superior effect on cognitive functions, and a greater ability to treat mood symptoms related to schizophrenia owing to their ability to act as antagonists to serotonin type-2A receptor (5-HT<sub>2A</sub>) (Celada et al., 2004). However, although being exempt of motor side effects, they are often associated with serious complications. For instance, sedation and weight gain are frequently observed in patients treated with atypical antipsychotics, especially with the onset of treatment and when high drug concentrations are used (Leo and Regno, 2000; Crossley et al., 2010). A rapid onset psychosis might also occur after treatment with atypical antipsychotics because of their relatively fast dissociation from dopamine D<sub>2</sub> receptors (Moncrieff, 2006). This phenomenon, termed 'rebound psychosis', has already been demonstrated and observed in several animal and human studies (Durst et al., 1999; Goudie et al., 1999), and is often associated with psychotic exacerbation and serious mental health deterioration.

In summary, although blockade of dopamine D2 receptors through the use of antipsychotics offers improvement in psychotic symptoms, several therapeutic needs remain unmet; all current antipsychotics have side effects and effort to minimise these should be encouraged.

#### 4. The ECS in schizophrenia

Because of major issues related to the use of antipsychotics, several studies have explored neurotransmitter systems outside of the standard dopamine hypothesis that could have potential implications in schizophrenia. One such system is the ECS. The belief that the ECS might be implicated in schizophrenia symptomatology comes from longitudinal studies suggesting that chronic exposure to cannabis, especially during adolescence, increases the risk of psychotic and schizophrenia-like symptoms later in life (Andreasson et al., 1987; Arseneault et al., 2002; Fergusson et al., 2003). Repeated use of cannabis results in the process of sensitization, whereby the behavioral and neurochemical effects of the drug are enhanced, leading to increased activation of the mesolimbic dopamine pathway (Murray et al., 2002; Pierce and Kumaresan, 2006). In schizophrenic patients, frequent cannabis use is associated with reduced AEA signalling, suggesting that alterations in the ECS might constitute an important risk factor for the development of schizophrenia-like symptoms (Leweke et al., 2007). Most of the psychomimetic effects of cannabis are due to the pharmacological actions of THC, which acts as a partial agonist of CB<sub>1</sub> and CB<sub>2</sub> receptors. Recent evidence has shown that THC administration in rats induces alterations in dopamine neurotransmission and increased psychomotor response to amphetamine (Ginovart et al., 2012). In addition, human neurochemical imaging studies reported increased striatal dopamine transmission after administration of THC to healthy participants, suggesting that cannabis use could constitute a primary biological mechanism underlying the associated higher risk of psychotic symptoms (Bossong et al., 2009; Bossong et al., 2015).

The notion that THC induces psychosis has raised the question as to whether cannabinoid receptors CB<sub>1</sub> and CB<sub>2</sub> are involved in the pathophysiology of schizophrenia. CB<sub>1</sub> and CB<sub>2</sub> receptors are G-protein coupled receptors that exert important physiological and behavioral functions. CB<sub>1</sub> receptors are located on central and peripheral neurons including glutamatergic projections to the hippocampus, the hypothalamus, the cortex and the cerebellum, whereas CB<sub>2</sub> receptors are primarily expressed by endothelial and immune cells (Pertwee, 2008; Schubart et al., 2014). AEA and 2-AG are the main endogenous ligands that bind to and activate cannabinoid receptors at specific synapses. Although being similarly distributed throughout the brain, they are found in relatively different concentrations. Brain concentrations of 2-AG are approximately 200-fold higher than those of AEA, with the highest level observed at the brainstem, medulla, limbic forebrain, striatum, and hippocampus (Basavarajappa, 2007). The main enzymes responsible for the degradation of AEA and 2-AG are FAAH and MAGL respectively. Although FAAH's mediated activity predominantly takes place in post-synaptic cells, MAGL-mediated degradation of 2-AG mainly occurs in pre-synaptic cells (Parsons and Hurd, 2015). 2-AG can also be catabolized by post-synaptic enzymes to a lesser extent, which include  $\alpha,\beta$ -hydrolase 6 (ABHD6), and ABHD12 (Blankman et al., 2007). Due to their unique role in regulating the level of endogenous ligands, these enzymes have been extensively studied over the past few years, and are being exploited as potential therapeutic targets for the treatment of schizophrenia (Petrosino and Di Marzo, 2010; Seillier et al., 2010).

Mounting evidence indicates that the ECS is significantly altered during the course of schizophrenia (Zamberletti et al., 2012; Fakhoury, 2016). Findings from neuroimaging and post-mortem studies have reported increased CB<sub>1</sub> receptor levels in the dorsolateral PFC (Dalton et

al., 2011; Jenko et al., 2012) and the posterior cingulate cortex (Newell et al., 2006) of schizophrenic patients. Increased CB<sub>1</sub> receptor activation inhibits the release of neurotransmitters such as glutamate and GABA, which are known to exert an inhibitory effect on the firing of dopaminergic neurons in the nucleus accumbens (Pertwee, 2008). On the other hand, post-mortem brain tissue analysis of schizophrenic patients revealed decreased AEA level in the hippocampus and cerebellum, and increased 2-AG level in the PFC (Muguruza et al., 2013). Similar findings were observed in the PFC of PCP-treated rats, a pharmacological-based animal model of schizophrenia (Vigano et al., 2009; Guidali et al., 2011). However, other studies have revealed an opposite phenomenon in schizophrenic patients. Namely, AEA levels were shown to be elevated in the peripheral blood (De Marchi et al., 2003; Leweke et al., 2012) and cerebrospinal fluid (CSF) (Leweke et al., 1999; Giuffrida et al., 2004; Leweke et al., 2007; Koethe et al., 2009) of schizophrenic patients. One possible explanation for such discrepancies is that the elevated AEA level in the blood and CSF, but not in the brain, of schizophrenic patients might occur as a result of adaptive changes to counteract the over-activation of dopamine D2 receptors (Leweke et al., 2012). Consistent with the notion, the increased peripheral level of AEA was shown to be reversed in schizophrenic patients who achieved clinical remission after antipsychotics therapy (De Marchi et al., 2003). However, despite the wide arrays of studies investigating the role of the ECS in schizophrenia, the neural circuit underpinning such relationship is far from being understood and needs further investigations.

### **5. CBD: a promising antipsychotic medication?**

Since the discovery of cannabinoid receptors and endogenous ligands, there has been growing interest in exploring the ECS as a new target for pharmacotherapy. Knowing that brain alterations in cannabinoid receptors and endocannabinoids are strongly associated with the development of psychotic symptoms, the use of selective compounds that regulate their levels may represent a promising avenue for schizophrenia research (Kucerova et al., 2014; Fakhoury, 2016). As it turned out, modulating the activity of the ECS holds great promise in the treatment of psychiatric disorders such as schizophrenia, but also in a wide range of other diseases and pathological conditions ranging from mood and movement disorders to cancer and metabolic syndromes (Pacher et al., 2006).

Evidence has shown that CBD exerts antipsychotic properties that could effectively be used in the treatment of schizophrenia (Zuardi et al., 2012; Iseger and Bossong, 2015). Compared to other known cannabinoids, CBD exhibits superior antipsychotic efficiency and is associated with limited side effects and low toxicity in humans and animals (Bergamaschi et al., 2011). CBD has been shown to behave as an inverse agonist of CB<sub>1</sub> and CB<sub>2</sub> receptors (Thomas et al., 2007; Pertwee, 2008), therefore providing a possible explanation for its ability to block THC-induced psychosis (Bhattacharyya et al., 2010; Niesink and van Laar, 2013). In addition, CBD was shown efficacious in reversing sensorimotor gating deficits in schizophrenia by acting as an agonist to the vanilloid 1 channel in the transient receptor potential family (TRPV1) (Long et al., 2006). CBD's antipsychotic properties are also largely explained by its ability to enhance AEA level through the inhibition of FAAH (Leweke et al., 2012). Indeed, FAAH inhibition, which could also be achieved with enzymes like URB597 or PF-3845, is considered as an attractive approach for ameliorating schizophrenia-like symptoms in rodents (Seillier et al., 2010; Seillier et al., 2013). Finally, CBD possesses anxiolytic and antidepressant-like effects owing to its ability to act as an agonist of 5-HT<sub>1A</sub> receptors (Zanelati et al., 2010; Gomes et al., 2011), thus making it efficient in treating mood symptoms related to schizophrenia.



Despite the increasing number of studies exploring the antipsychotic properties of CBD, there are still debates as to whether it should be used in the treatment of schizophrenia. Therefore, to review the current state of knowledge of CBD in schizophrenia, the following sections provide a summary of findings from animal studies and clinical trials investigating the antipsychotic properties and side-effect profile of this plant-derived cannabinoid.

### 5.1 Evidence from animal models

A wide array of studies, summarized in **Table 1**, have investigated the antipsychotic effects of CBD in animal models of schizophrenia-like symptoms. One of the most widely used model for the positive symptoms of schizophrenia is drug-induced locomotor hyperactivity (van den Buuse, 2010). An increased response to psychomotor stimulants, such as D-amphetamine, is often observed in rodent models of schizophrenia, and is indicative of changes in impulse-dependent dopamine neuron activity (Gill et al., 2011; Perez et al., 2013). Unlike haloperidol but similar to clozapine, CBD reverses the hyperlocomotion induced by D-amphetamine or ketamine in mice without causing catalepsy (Moreira and Guimaraes, 2005). CBD also presents a lower risk of developing unwanted side effects such as high level of prolactin when compared to haloperidol (Zuardi et al., 1991), suggesting that it might share a similar therapeutic profile with atypical antipsychotics.

Although several studies were able to further exemplify the potential of CBD in reversing drug-induced hyperlocomotion in rodents (Malone et al., 2009; Long et al., 2010), others have failed to observe such an effect (Gururajan et al., 2011; Valvassori et al., 2011). For instance, the increase in locomotor activity triggered by MK-801, an NMDA receptor antagonist, remained unchanged following CBD administration (Gururajan et al., 2011). In addition, acute but not chronic treatment of CBD failed to reduce Dexamphetamine-induced hyperlocomotion in mice (Long et al., 2010). Although the bases for the apparently different results may in part be explained by differences in rodent species and drug regimen, these discrepancies raise question of methodological accuracy and indicate a priority need for more research.

Contradictory results were also observed with regards to the effect of CBD on the prepulse inhibition (PPI) of the startle response. PPI is a neurological measure reflecting sensorimotor gating, and is defined as a reduction of the startle reflex when the intense startling stimulus is preceded by a weaker nonstartling prepulse (Li et al., 2009). Impairments in PPI are often observed in animal models of schizophrenia as well as in patients with psychotic-like symptoms, and reflect the reduced ability to filter out non-relevant sensory stimuli (Geyer et al., 2001; Swerdlow et al., 2006; Lodge and Grace, 2009). In mice, CBD was successfully able to reverse the deficits in PPI induced by MK-801 (Long et al., 2006). However, these results failed to be replicated in a MK-801-induced rat model of schizophrenia (Gururajan et al., 2011), suggesting that the effect of CBD may vary between different rodent species.

CBD treatment was also shown to attenuate psychostimulant-induced social withdrawal, a parameter that mirrors well the negative symptoms of schizophrenia (Malone et al., 2009; Gururajan et al., 2011). Although no effect was observed in Spontaneously Hypertensive Rats (SHRs), CBD was still able to increase passive and total social interaction in control rats, supporting an anxiolytic profile of this compound (Almeida et al., 2013). In addition, CBD shows great potential in ameliorating the cognitive deficits related to schizophrenia, as evidenced by its ability to reverse THC-induced impairments of visuospatial associative memory in rhesus monkeys (Wright et al., 2013). However, despite the proven efficacy of CBD in alleviating psychostimulant-induced cognitive deficits, additional studies using animal models of complex

cognitive functions are needed prior to drawing any reliable conclusions regarding its therapeutic use.

## 5.2 Evidence from clinical trials

A summary of clinical trials that have investigated the antipsychotic effects of CBD in patients with psychotic symptoms is illustrated in **Table 2**. Due to ethical issues related to the use of cannabis-derived compounds, the first few clinical trials with CBD consisted of open trials with a small number of patients. In 1995, Zuardi et al. (1995) reported on a case report evaluating the antipsychotic effects of CBD in a 19-year old female patient with schizophrenia, who was previously experiencing severe side effects with antipsychotic medications. The main finding of this study was that CBD monotherapy (up to 1500 mg/day for 4 weeks) was able to significantly reduce the scores of the Brief Psychiatric Rating Scale (BPRS) (Zuardi et al., 1995). Although no side effects were observed during the treatment, there was a worsening of the symptoms following CBD discontinuation (Zuardi et al., 1995). In a subsequent open-label trial of three treatment-resistant schizophrenic patients, CBD administration (from 40 to 1280 mg/day for 30 days) resulted in improved symptomatology in one case only (Zuardi et al., 2006), whereas in another study, oral administration of CBD was shown to successfully reduce the symptoms of psychosis in all six out-patients with Parkinson's disease (PD) (Zuardi et al., 2009).

The first double-blind trial with CBD was aimed at investigating its effects on selective attention and psychotic symptoms in 28 patients with schizophrenia (Hallak et al., 2010). In this study, patients were evaluated with the BPRS and the Positive And Negative Syndrome Scale (PANSS), and submitted to the Stroop Color Word Test (SCWT). They were then divided into three groups that would receive a single dose of either placebo, CBD (300mg) or CBD (600mg). Although CBD at a dose of 300mg improved the results obtained in the SCWT, no differences were observed compared to patients who received placebo (Hallak et al., 2010). In addition, the single, acute administration of the highest dose of CBD failed to have a significant effect on the performance of patients in the SCWT, and no effects of CBD administration were found on symptomatology (Hallak et al., 2010).

In another double-blind study, Leweke et al., (2011) performed a cross-over clinical trial evaluating the efficacy of CBD in the treatment of antipsychotic-naïve, first-episode schizophrenic patients. All patients received a single dose of either CBD (600 mg) or placebo for 14 days, and were then switched to the corresponding cross-over condition (Leweke et al., 2011). Among the 29 patients who were initially enrolled in the study, 18 patients completed the 28 days of treatment with significant reductions in psychotic symptoms (Leweke et al., 2011). The same group has also conducted a double-blind, randomized clinical trial of CBD versus the atypical antipsychotic amisulpride in 42 patients with schizophrenia or schizophreniform disorder for 4 weeks (Leweke et al., 2012). Although both CBD and amisulpride (up to 800 mg/day, oral) resulted in a distinct attenuation of psychotic symptoms, CBD treatment was accompanied by smaller changes in extrapyramidal side effects including weight gain and increased prolactin level (Leweke et al., 2012).

Taken together, these clinical trials yielded in general positive results, in that the majority of patients treated with CBD displayed notable reduction in psychotic symptoms. However, one limitation of these studies is that the duration of the trials were relatively short (up to 30 days) and insufficient to determine the long-term antipsychotic effect of the treatment. Clinical trials of

longer duration need to be conducted to evaluate the safety and tolerability of CBD in schizophrenic patients, and to determine whether this cannabinoid could be used as an alternative for current antipsychotic treatment.

## 6. Conclusion

Despite significant progress in research, schizophrenia remains a debilitating disorder that presents a serious challenge to clinical therapeutics. As antipsychotics failed to meet expectations, the search for more effective therapies is still under way. The studies presented in this paper have shown that CBD could effectively reverse the positive, negative and cognitive symptoms of schizophrenia in animal models of the disease. In addition, findings from clinical trials suggest that CBD is safe to use in patients with schizophrenia, even at high doses, and that it offers a more appealing side-effect profile compared to antipsychotic drugs. However, although recent research has shaped our understanding of the therapeutic profile of CBD in schizophrenia, there are still missing gaps in the literature that need to be addressed. More particularly, all of the animal studies investigating the antipsychotic effects of CBD have used drug-induced models of schizophrenia instead of neurodevelopmental models, which seem to better reflect the behavioral and functional deficits observed in individuals with schizophrenia (Wilson and Terry, 2010). Future studies should therefore focus on using appropriate neurodevelopmental animal models of schizophrenia to investigate the antipsychotic effect of CBD. Clinical trials of longer duration are also needed to provide a more reliable comparison of the therapeutic profile of CBD with those of currently used medications. This will help determine whether CBD could be used as a first line of treatment in patients with schizophrenia.

## References

- Alex KD, Pehek EA (2007) Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacol Ther* 113:296-320.
- Almeida V, Levin R, Peres FF, Niigaki ST, Calzavara MB, Zuardi AW, Hallak JE, Crippa JA, Abilio VC (2013) Cannabidiol exhibits anxiolytic but not antipsychotic property evaluated in the social interaction test. *Prog Neuropsychopharmacol Biol Psychiatry* 41:30-35.
- Andreasson S, Allebeck P, Engstrom A, Rydberg U (1987) Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* 2:1483-1486.
- Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE (2002) Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 325:1212-1213.
- Balla A, Koneru R, Smiley J, Sershen H, Javitt DC (2001) Continuous phencyclidine treatment induces schizophrenia-like hyperreactivity of striatal dopamine release. *Neuropsychopharmacology* 25:157-164.
- Basavarajappa BS (2007) Neuropharmacology of the endocannabinoid signaling system-molecular mechanisms, biological actions and synaptic plasticity. *Curr Neuropharmacol* 5:81-97.
- Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA (2011) Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Curr Drug Saf* 6:237-249.

- Bhattacharyya S, Raote I, Bhattacharya A, Miledi R, Panicker MM (2006) Activation, internalization, and recycling of the serotonin 2A receptor by dopamine. *Proc Natl Acad Sci U S A* 103:15248-15253.
- Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, CM OC, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* 35:764-774.
- Bhugra D (2004) Migration, distress and cultural identity. *Br Med Bull* 69:129-141.
- Bhugra D, Becker MA (2005) Migration, cultural bereavement and cultural identity. *World Psychiatry* 4:18-24.
- Blankman JL, Simon GM, Cravatt BF (2007) A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. *Chem Biol* 14:1347-1356.
- Bossong MG, Mehta MA, van Berckel BN, Howes OD, Kahn RS, Stokes PR (2015) Further human evidence for striatal dopamine release induced by administration of 9-tetrahydrocannabinol (THC): selectivity to limbic striatum. *Psychopharmacology (Berl)* 232:2723-2729.
- Bossong MG, van Berckel BN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, van Gerven JM, Ramsey NF, Lammertsma AA, Kahn RS (2009) Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology* 34:759-766.
- Brisch R, Saniotis A, Wolf R, Bielau H, Bernstein HG, Steiner J, Bogerts B, Braun K, Jankowski Z, Kumaratilake J, Henneberg M, Gos T (2014) The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. *Front Psychiatry* 5:47.
- Caspi A, Davidson M, Tamminga CA (2004) Treatment-refractory schizophrenia. *Dialogues Clin Neurosci* 6:61-70.
- Celada P, Puig M, Amargos-Bosch M, Adell A, Artigas F (2004) The therapeutic role of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors in depression. *J Psychiatry Neurosci* 29:252-265.
- Crossley NA, Constante M, McGuire P, Power P (2010) Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. *Br J Psychiatry* 196:434-439.
- D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 29:1558-1572.
- D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 57:594-608.
- Dalton VS, Long LE, Weickert CS, Zavitsanou K (2011) Paranoid schizophrenia is characterized by increased CB1 receptor binding in the dorsolateral prefrontal cortex. *Neuropsychopharmacology* 36:1620-1630.
- De Marchi N, De Petrocellis L, Orlando P, Daniele F, Fezza F, Di Marzo V (2003) Endocannabinoid signalling in the blood of patients with schizophrenia. *Lipids Health Dis* 2:5.

- Di Pietro NC, Seamans JK (2007) Dopamine and serotonin interactions in the prefrontal cortex: insights on antipsychotic drugs and their mechanism of action. *Pharmacopsychiatry* 40 Suppl 1:S27-33.
- Dold M, Samara MT, Li C, Tardy M, Leucht S (2015) Haloperidol versus first-generation antipsychotics for the treatment of schizophrenia and other psychotic disorders. *Cochrane Database Syst Rev* 1:CD009831.
- Durst R, Teitelbaum A, Katz G, Knobler HY (1999) Withdrawal from clozapine: the "rebound phenomenon". *Isr J Psychiatry Relat Sci* 36:122-128.
- Fakhoury M (2016) Role of the Endocannabinoid System in the Pathophysiology of Schizophrenia. *Mol Neurobiol*.
- Fergusson DM, Horwood LJ, Swain-Campbell NR (2003) Cannabis dependence and psychotic symptoms in young people. *Psychol Med* 33:15-21.
- Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology (Berl)* 156:117-154.
- Gill KM, Lodge DJ, Cook JM, Aras S, Grace AA (2011) A novel alpha5GABA(A)R-positive allosteric modulator reverses hyperactivation of the dopamine system in the MAM model of schizophrenia. *Neuropsychopharmacology* 36:1903-1911.
- Ginovart N, Kapur S (2012) Role of dopamine D(2) receptors for antipsychotic activity. *Handb Exp Pharmacol*:27-52.
- Ginovart N, Tournier BB, Moulin-Sallanon M, Steimer T, Ibanez V, Millet P (2012) Chronic Delta(9)-tetrahydrocannabinol exposure induces a sensitization of dopamine D(2)/(3) receptors in the mesoaccumbens and nigrostriatal systems. *Neuropsychopharmacology* 37:2355-2367.
- Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, Klosterkötter J, Piomelli D (2004) Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. *Neuropsychopharmacology* 29:2108-2114.
- Gomes FV, Resstel LB, Guimaraes FS (2011) The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. *Psychopharmacology (Berl)* 213:465-473.
- Goudie AJ, Smith JA, Robertson A, Cavanagh C (1999) Clozapine as a drug of dependence. *Psychopharmacology (Berl)* 142:369-374.
- Guidali C, Vigano D, Petrosino S, Zamberletti E, Realini N, Binelli G, Rubino T, Di Marzo V, Parolaro D (2011) Cannabinoid CB1 receptor antagonism prevents neurochemical and behavioural deficits induced by chronic phencyclidine. *Int J Neuropsychopharmacol* 14:17-28.
- Gururajan A, Taylor DA, Malone DT (2011) Effect of cannabidiol in a MK-801-rodent model of aspects of schizophrenia. *Behav Brain Res* 222:299-308.
- Hallak JE, Machado-de-Sousa JP, Crippa JA, Sanches RF, Trzesniak C, Chaves C, Bernardo SA, Regalo SC, Zuardi AW (2010) Performance of schizophrenic patients in the Stroop Color Word Test and electrodermal responsiveness after acute administration of cannabidiol (CBD). *Rev Bras Psiquiatr* 32:56-61.
- Howes OD, Kapur S (2009) The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull* 35:549-562.

- Iseger TA, Bossong MG (2015) A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophr Res* 162:153-161.
- Jenko KJ, Hirvonen J, Henter ID, Anderson KB, Zoghbi SS, Hyde TM, Deep-Soboslay A, Innis RB, Kleinman JE (2012) Binding of a tritiated inverse agonist to cannabinoid CB1 receptors is increased in patients with schizophrenia. *Schizophr Res* 141:185-188.
- Kapur S, Seeman P (2001) Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. *Am J Psychiatry* 158:360-369.
- Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL, Cooper TB, Carlsson A, Laruelle M (2000) Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biol Psychiatry* 48:627-640.
- Koethe D, Giuffrida A, Schreiber D, Hellmich M, Schultze-Lutter F, Ruhrmann S, Klosterkötter J, Piomelli D, Leweke FM (2009) Anandamide elevation in cerebrospinal fluid in initial prodromal states of psychosis. *Br J Psychiatry* 194:371-372.
- Kucerova J, Tabiova K, Drago F, Micale V (2014) Therapeutic potential of cannabinoids in schizophrenia. *Recent Pat CNS Drug Discov* 9:13-25.
- Kwek P, van den Buuse M (2013) Modafinil disrupts prepulse inhibition in mice: strain differences and involvement of dopaminergic and serotonergic activation. *Eur J Pharmacol* 699:132-140.
- Lambert M, Schimmelmann BG, Schacht A, Suarez D, Haro JM, Novick D, Wagner T, Wehmeier PM, Huber CG, Hundemer HP, Dittmann RW, Naber D (2011) Differential 3-year effects of first- versus second-generation antipsychotics on subjective well-being in schizophrenia using marginal structural models. *J Clin Psychopharmacol* 31:226-230.
- Leo RJ, Regno PD (2000) Atypical Antipsychotic Use in the Treatment of Psychosis in Primary Care. *Prim Care Companion J Clin Psychiatry* 2:194-204.
- Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D (1999) Elevated endogenous cannabinoids in schizophrenia. *Neuroreport* 10:1665-1669.
- Leweke FM, Kranaster L, Pahlisch F, Klosterkötter J, Hellmich M, Piomelli D, Koethe D (2011) The efficacy of cannabidiol in the treatment of schizophrenia - a translational approach. *Schizophr Bull* 37.
- Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M, Koethe D (2012) Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2:e94.
- Leweke FM, Giuffrida A, Koethe D, Schreiber D, Nolden BM, Kranaster L, Neatby MA, Schneider M, Gerth CW, Hellmich M, Klosterkötter J, Piomelli D (2007) Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use. *Schizophr Res* 94:29-36.
- Li L, Du Y, Li N, Wu X, Wu Y (2009) Top-down modulation of prepulse inhibition of the startle reflex in humans and rats. *Neurosci Biobehav Rev* 33:1157-1167.
- Lieberman JA (2004) Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs* 18:251-267.
- Lodge DJ, Grace AA (2009) Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. *Behav Brain Res* 204:306-312.
- Long LE, Malone DT, Taylor DA (2006) Cannabidiol reverses MK-801-induced disruption of prepulse inhibition in mice. *Neuropsychopharmacology* 31:795-803.

- Long LE, Chesworth R, Huang XF, McGregor IS, Arnold JC, Karl T (2010) A behavioural comparison of acute and chronic Delta9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. *Int J Neuropsychopharmacol* 13:861-876.
- Makinen J, Miettunen J, Isohanni M, Koponen H (2008) Negative symptoms in schizophrenia: a review. *Nord J Psychiatry* 62:334-341.
- Malone DT, Jongejan D, Taylor DA (2009) Cannabidiol reverses the reduction in social interaction produced by low dose Delta(9)-tetrahydrocannabinol in rats. *Pharmacol Biochem Behav* 93:91-96.
- Mathews M, Gratz S, Adetunji B, George V, Mathews M, Basil B (2005) Antipsychotic-induced movement disorders: evaluation and treatment. *Psychiatry (Edgmont)* 2:36-41.
- McGrath J, Saha S, Chant D, Welham J (2008) Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* 30:67-76.
- Miller R (2009) Mechanisms of action of antipsychotic drugs of different classes, refractoriness to therapeutic effects of classical neuroleptics, and individual variation in sensitivity to their actions: Part I. *Curr Neuropharmacol* 7:302-314.
- Moller M, Du Preez JL, Viljoen FP, Berk M, Emsley R, Harvey BH (2013) Social isolation rearing induces mitochondrial, immunological, neurochemical and behavioural deficits in rats, and is reversed by clozapine or N-acetyl cysteine. *Brain Behav Immun* 30:156-167.
- Moncrieff J (2006) Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand* 114:3-13.
- Moreira FA, Guimaraes FS (2005) Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. *Eur J Pharmacol* 512:199-205.
- Morken G, Widen JH, Grawe RW (2008) Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. *BMC Psychiatry* 8:32.
- Muguruza C, Lehtonen M, Aaltonen N, Morentin B, Meana JJ, Callado LF (2013) Quantification of endocannabinoids in postmortem brain of schizophrenic subjects. *Schizophr Res* 148:145-150.
- Murray RM, McDonald C, Bramon E (2002) Neurodevelopmental impairment, dopamine sensitisation, and social adversity in schizophrenia. *World Psychiatry* 1:137-145.
- Newell KA, Deng C, Huang XF (2006) Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. *Exp Brain Res* 172:556-560.
- Niesink RJ, van Laar MW (2013) Does Cannabidiol Protect Against Adverse Psychological Effects of THC? *Front Psychiatry* 4:130.
- Pacher P, Batkai S, Kunos G (2006) The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 58:389-462.
- Parsons LH, Hurd YL (2015) Endocannabinoid signalling in reward and addiction. *Nat Rev Neurosci* 16:579-594.
- Patel KR, Cherian J, Gohil K, Atkinson D (2014) Schizophrenia: overview and treatment options. *P T* 39:638-645.
- Perez SM, Shah A, Asher A, Lodge DJ (2013) Hippocampal deep brain stimulation reverses physiological and behavioural deficits in a rodent model of schizophrenia. *Int J Neuropsychopharmacol* 16:1331-1339.
- Pertwee RG (2008) The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol* 153:199-215.

- Petrosino S, Di Marzo V (2010) FAAH and MAGL inhibitors: therapeutic opportunities from regulating endocannabinoid levels. *Curr Opin Investig Drugs* 11:51-62.
- Pierce RC, Kumaresan V (2006) The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neurosci Biobehav Rev* 30:215-238.
- Ramachandiraiah CT, Subramaniam N, Tancer M (2009) The story of antipsychotics: Past and present. *Indian J Psychiatry* 51:324-326.
- Remington G (2008) Alterations of dopamine and serotonin transmission in schizophrenia. *Prog Brain Res* 172:117-140.
- Schubart CD, Sommer IE, Fusar-Poli P, de Witte L, Kahn RS, Boks MP (2014) Cannabidiol as a potential treatment for psychosis. *Eur Neuropsychopharmacol* 24:51-64.
- Seeman P (2011) All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D2(high) receptors. *CNS Neurosci Ther* 17:118-132.
- Seeman P, Lee T (1975) Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* 188:1217-1219.
- Seeman P, Weinshenker D, Quirion R, Srivastava LK, Bhardwaj SK, Grandy DK, Premont RT, Sotnikova TD, Boksa P, El-Ghundi M, O'Dowd B F, George SR, Perreault ML, Mannisto PT, Robinson S, Palmiter RD, Talerico T (2005) Dopamine supersensitivity correlates with D2High states, implying many paths to psychosis. *Proc Natl Acad Sci U S A* 102:3513-3518.
- Seillier A, Martinez AA, Giuffrida A (2013) Phencyclidine-induced social withdrawal results from deficient stimulation of cannabinoid CB(1) receptors: implications for schizophrenia. *Neuropsychopharmacology* 38:1816-1824.
- Seillier A, Advani T, Cassano T, Hensler JG, Giuffrida A (2010) Inhibition of fatty-acid amide hydrolase and CB1 receptor antagonism differentially affect behavioural responses in normal and PCP-treated rats. *Int J Neuropsychopharmacol* 13:373-386.
- Sheffield JM, Gold JM, Strauss ME, Carter CS, MacDonald AW, 3rd, Ragland JD, Silverstein SM, Barch DM (2014) Common and specific cognitive deficits in schizophrenia: relationships to function. *Cogn Affect Behav Neurosci* 14:161-174.
- Swerdlow NR, Light GA, Cadenhead KS, Sprock J, Hsieh MH, Braff DL (2006) Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition, and level of function. *Arch Gen Psychiatry* 63:1325-1335.
- Tandon R, Jibson MD (2002) Extrapyramidal side effects of antipsychotic treatment: scope of problem and impact on outcome. *Ann Clin Psychiatry* 14:123-129.
- Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG (2007) Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol* 150:613-623.
- Ucok A, Gaebel W (2008) Side effects of atypical antipsychotics: a brief overview. *World Psychiatry* 7:58-62.
- 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 (2011) Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania. *J Psychopharmacol* 25:274-280.
- van den Buuse M (2010) Modeling the positive symptoms of schizophrenia in genetically modified mice: pharmacology and methodology aspects. *Schizophr Bull* 36:246-270.



- Vigano D, Guidali C, Petrosino S, Realini N, Rubino T, Di Marzo V, Parolaro D (2009) Involvement of the endocannabinoid system in phencyclidine-induced cognitive deficits modelling schizophrenia. *Int J Neuropsychopharmacol* 12:599-614.
- Wilson C, Terry AV, Jr. (2010) Neurodevelopmental animal models of schizophrenia: role in novel drug discovery and development. *Clin Schizophr Relat Psychoses* 4:124-137.
- Wright MJ, Jr., Vandewater SA, Taffe MA (2013) Cannabidiol attenuates deficits of visuospatial associative memory induced by Delta(9) tetrahydrocannabinol. *Br J Pharmacol* 170:1365-1373.
- Zamberletti E, Rubino T, Parolaro D (2012) The endocannabinoid system and schizophrenia: integration of evidence. *Curr Pharm Des* 18:4980-4990.
- Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SR (2010) Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol* 159:122-128.
- Zuardi AW, Rodrigues JA, Cunha JM (1991) Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacology (Berl)* 104:260-264.
- Zuardi AW, Morais SL, Guimaraes FS, Mechoulam R (1995) Antipsychotic effect of cannabidiol. *J Clin Psychiatry* 56:485-486.
- Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE, Crippa JA (2006) Cannabidiol monotherapy for treatment-resistant schizophrenia. *J Psychopharmacol* 20:683-686.
- Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, Dursun SM, Tumas V (2009) Cannabidiol for the treatment of psychosis in Parkinson's disease. *J Psychopharmacol* 23:979-983.
- Zuardi AW, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, McGuire PK, Guimaraes FS (2012) A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. *Curr Pharm Des* 18:5131-5140.

**Acknowledgments**

The author is recipient of an award from the Natural Sciences and Engineering Research Council (NSERC) of Canada.

ACCEPTED MANUSCRIPT

Animal	Model	Drug (doses mg/kg)	Effective doses	References
<b>Locomotor activity</b>				
Male Swiss mice	D-amphetamine-induced hyperlocomotion	CBD (15, 30, 60, i.p.) Haloperidol (0.15, 0.3, 0.6, i.p.) Clozapine (1.25, 2.5, 5, s.c.)	30, 60 0.15, 0.3, 0.6 5	Moreira and Guimaraes, 2005
	ketamine-induced hyperlocomotion	CBD (15, 30, 60 i.p.) Haloperidol (0.15, 0.3, 0.6, i.p.) Clozapine (1.25, 2.5, 5, s.c.)	30 0.3, 0.6 1.25, 2.5, 5	
Male Sprague–Dawley rats	THC-induced hyperlocomotion	CBD (5, 20, i.p.)	20	Malone et al., 2009
Male C57BL/6J Arc mice	Dexamphetamine-induced hyperlocomotion	CBD (1, 50, i.p) acute	-	Long et al., 2010
		CBD (1, 5, 10, 50) for 21 days	50	
Male Wistar rats	D-amphetamine-induced hyperlocomotion	CBD (15, 30, 60, i.p.) twice a day for 7 or 14 days	-	Valvassori et al., 2011
Male Sprague–Dawley rats	MK-801-induced hyperlocomotion	CBD (3, 10, 30, i.p.)	-	Guruja et al., 2011
		Clozapine (1, 3, 10, i.p)	3, 10	
<b>PPI disruption</b>				
Male Swiss mice	MK-801-induced PPI disruption	CBD (5, i.p.)	5	Long et al., 2006
		Clozapine (4, i.p.)	4	
Male Sprague–Dawley rats	MK-801-induced PPI disruption	CBD (3, 10, 30, ip)	-	Guruja et al., 2011
		Clozapine (1, 3, 10, ip)	-	
<b>Social interaction</b>				
Male Sprague–Dawley rats	THC-induced social withdrawal	CBD (5, 20, i.p.)	20	Malone et al., 2009
Male Sprague–Dawley rats	MK-801-induced social withdrawal	CBD (3, 10, 30, i.p.)	3, 10	Guruja et al., 2011
		Clozapine (1, 3, 10, i.p)	1, 3	
Spontaneously Hypertensive Rats (SHRs)	Social withdrawal	CBD (1-60, i.p.)	-	Almeida et al., 2013
<b>Cognitive functions</b>				
Male rhesus monkeys	THC-induced cognitive impairments	CBD (0.5, i.m.)	0.5	Wright et al., 2013
<b>Side effects</b>				
Rats	Catalepsy	CBD (60, 120, 240, 480)	-	Zuardi et al., 1991
		Haloperidol (0.125, 0.25, 0.5, 1.0)	0.25, 0.5, 1.0	
	Increased prolactin levels	CBD (15, 30, 60, 120, 240)	240	
		Haloperidol (0.06, 0.125, 0.25, 0.5)	0.125, 0.25, 0.5	
Male Swiss mice	Catalepsy	CBD (15, 30, 60 i.p.)	-	Moreira and Guimaraes, 2005
		Haloperidol (0.15, 0.3, 0.6, i.p.)	0.15, 0.3, 0.6	
		Clozapine (1.25, 2.5, 5, s.c.)	-	

**Table 1:** Animal studies evaluating the antipsychotic profile and side effects of CBD. Abbreviations: i.p. intraperitoneal; s.c. subcutaneous; i.m. intramuscular

Patients	Type of study	Drug regimen (dose, route)	Assessment	Main findings	References
19-year old female patient with schizophrenia	Open trial	CBD (up to 1500 mg/day, oral) for 4 weeks	BPRS	Improvement of symptomatology with no side effects	Zuardi et al., 1995
3 treatment-resistant patients with schizophrenia	Open trial	CBD (up to 1280 mg/day, oral) for 30 days	BPRS	Improvement of symptomatology in one patient	Zuardi et al., 2006
6 Parkinson's disease patients with psychotic symptoms	Open trial	CBD (150 to 400 mg/day, oral) for 4 weeks in combination with antiparkinsonian drug	BPRS, PPQ	Improvement of symptomatology with no side effects	Zuardi et al., 2009
28 schizophrenic patients	Double-blind	Single doses of CBD (300 or 600 mg, oral) or placebo	SCWT, BPRS, PANSS	Increased performance in the SCWT after placebo and CBD (300 mg); No improvement of symptomatology	Hallak et al., 2010
29 first-episode onset schizophrenia patients	Double-blind Cross-over	CBD (600 mg/day, oral) versus placebo for 28 days	BPRS, PANSS	18 patients completed the trial with a significant improvement in psychotic symptoms	Leweke et al., 2011
42 patients with schizophrenia or schizophreniform disorder	Double-blind	CBD versus amisulpride (up to 800 mg/day, oral) for 4 weeks	BPRS, PANSS	Improvement of symptomatology with both CBD or amisulpride; Less side effects with CBD	Leweke et al., 2012

**Table 2:** Clinical trials evaluating the effect of CBD in patients with psychotic symptoms. Abbreviations: BPRS: Brief Psychiatric Rating Scale; PPQ: Parkinson Psychosis Questionnaire; SCWT: Stroop Color-Word Test; PANSS: Positive And Negative Syndrome Scale

- Antipsychotics failed to meet expectations because of their severe side effects
- The endocannabinoid system is increasingly recognized as having a role in schizophrenia
- Herein, I review the antipsychotic effects of CBD in clinical trials and animal models of schizophrenia
- CBD exhibits potent antipsychotic properties and a superior side-effect profile

**Contributor**  
Marc Fakhoury

ACCEPTED MANUSCRIPT

**Role of the Funding Source**

Not available for this type of study

ACCEPTED MANUSCRIPT