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Review: The Efficacy of Cannabidiol (CBD) as Potential Antipsychotic Medication

Review

Psychotic disorders such as schizophrenia are widespread and severely disabling; however, current pharmacological treatments are unsatisfactory due to major side effects. The current review discusses the therapeutic potential of cannabidiol (CBD), a non-psychoactive component of cannabis, as an antipsychotic drug. Research lines including studies based on animal models of psychosis, human experimental studies, neuroimaging studies, epidemiological studies, and clinical studies are reviewed. The studies described provide empirical support for the antipsychotic effects of CBD and indicate reduced side effects, high tolerability, and superior cost-effectiveness compared to regular antipsychotic medication. It is concluded that CBD may prove a safe and attractive alternative treatment for psychotic conditions. However, current evidence largely stems from experimental, non-clinical studies. Large-scale randomized clinical trials are needed before this can be implemented in practice.

Keywords: schizophrenia, treatment, cannabidiol, antipsychotics

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INTRODUCTION

Schizophrenia is a chronic, debilitating mental disorder that affects 0.7 percent of the world's population (Tandon, Nasrallah, & Keshavan, 2008). It is characterized by a highly heterogeneous clinical manifestation of positive (e.g., delusions, hallucinations), negative (e.g., apathy, blunted affect), cognitive (e.g., impaired executive function, working memory), disorganization (e.g., formal thought disorder), psychomotor (e.g., catatonia) and mood (e.g., increased arousal, depression) symptoms, whereby official diagnosis requires the presence of at least two major symptoms for a minimum period of one month (American Psychiatric Association, 2013). Onset of psychotic symptoms is usually in adolescence or early adulthood, and genetic factors contribute over 80% of the liability for developing schizophrenia (Tandon et al., 2008). It tends to be a chronic and relapsing condition with generally incomplete remissions, and is associated with shortened lifespan and significant impairments in social and vocational functioning (e.g., reduced employment rates, increased incarceration and homelessness rates; Rössler, Salize, van Os, Riecher-Rössler, 2005).

The cornerstone of treatment for schizophrenia is pharmacological therapy, and the common mechanism of most antipsychotic drugs is the blockage of dopamine D2 receptors (Gardner, Balsdessarini, & Waraich, 2005). However, current antipsychotic medication is only partially effective – it improves positive symptoms but is less effective for negative symptoms – and is associated with frequent serious side effects (Tandon, Nasrallah, & Keshavan, 2010). Typical antipsychotic drugs (first-generation antipsychotics) commonly induce extrapyramidal side effects (Parkinson-like motor disturbances), stemming from dopamine depletion of the nigrostriatal pathway due to continued consumption of the medication (Stahl, 2001). Atypical antipsychotics (second-generation antipsychotics) may lead to fewer extrapyramidal side effects, but carry other adverse consequences such as increased risk for cardiovascular disease, sexual dysfunction, and significant weight gain. A large proportion of patients fail to adhere to

pharmacological antipsychotic treatment due to such tolerability issues (Leucht, Heres, Kissling, & Davis, 2011). Consequently, there is a persistent need for new treatment options against schizophrenia that are both safe and effective.

However, this search is impeded by the complex pathogenesis of the disorder, which is known to involve multiple brain neurotransmitter systems (Rogers & Goldsmith, 2009). Besides the dopaminergic, serotonergic, and glutamatergic systems, recent findings indicate that the human endogenous cannabinoid system is significantly involved in the development of schizophrenia. Specifically, administration of ⵠ9-tetrahydrocannabinol (THC), which is the main psychoactive compound of cannabis, can acutely induce transient psychotic-like symptoms in healthy volunteers, and exacerbate psychotic symptoms in schizophrenic patients (D'Souza et al., 2005). Moreover, the use of cannabis has been reported to increase the risk for developing a psychotic disorder (e.g., Moore et al., 2007), although methodological issues across studies raise obstacles to definite statements of a causal relationship (McLaren, Silins, Hutchinson, Mattick, & Hall, 2010). On the other hand, cannabis has been implicated in medicinal use since prehistoric times (e.g., against inflammatory conditions and asthma; Schubart et al., 2014), and it may in fact carry both a risk and a remedy for psychotic conditions in itself: Cannabidiol (CBD) is a non-psychoactive component of cannabis, and the natural counterpart of THC (Mechoulam, Peters, Murillo-Rodriguez, & Hanus, 2007). The concentration of these two major cannabinoids in cannabis appears to follow an inverse relationship. In 1974, it was reported that CBD could counteract the psychotomimetic and anxiety- inducing effects of THC (Karniol et al., 1974), providing a first indication of its antipsychotic and anxiolytic properties. Interest in CBD's medicinal benefits has been growing since, and evidence is accumulating for its potential as an antipsychotic agent. The current review aims to provide an overview and an evaluation of the evidence-base of CBD as an antipsychotic agent.

The pharmacological mechanism through which cannabidiol exerts its antipsychotic effects is currently not fully understood, but there is evidence for multiple mechanisms of action.

Despite its low affinity for CB1 and CB2 receptors, CBD is capable of antagonizing CB1/CB2 receptor agonists (such as THC and the two main endocannabinoids 2-arachidonoylglycerol and anandamide) at relatively low concentrations (Pertwee, 2008). Other mechanisms of action include antagonism of the recently discovered GPR55 receptor; transient receptor potential vanilloid type 1 (TRPV1) agonism; transient receptor potential vanilloid type 2 (TRPV2) agonism; modest affinity agonism of the 5-HT1A serotonin receptor; antagonism of the putative abnormal-CBD receptor; and regulation of intracellular [Ca2+] (Izzo, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009; Russo, Burnett, Hall, & Parker, 2005). Moreover, there is evidence that CBD blocks the degradation of anandamide (AEA) by inhibiting the fatty acide amine hydrolase (FAAH) enzyme, which is the main metabolite of AEA, thereby enhancing AEA levels in the brain (Bisogno et al., 2001). Leweke and colleagues (2012) found that an increase in AEA levels was associated with a decrease in psychotic symptoms in patients treated with CBD. Moreover, cerebrospinal anandamide levels were found to be significantly higher in schizophrenia patients relative to healthy subjects, but they correlated negatively with psychotic symptoms (Giuffrida et al., 2004). Therefore, it was proposed that anandamide release might serve as an adaptive compensatory mechanism during acute psychoses, representing a negative feedback response to overactivation of dopamine D2 receptors (Leweke et al., 2007).

Evaluating the evidence for the efficacy of cannabidiol (CBD) as potential antipsychotic medication

Several lines of evidence suggest that CBD has potential as an antipsychotic treatment. These include studies based on animal models of psychosis, human experimental studies, neuroimaging studies, epidemiological studies, and clinical studies.

Animal studies

Animal models employing behavioral as well as neurochemical methodology suggest that CBD has a pharmacological profile similar to that of an atypical antipsychotic drug (Zuardi, Crippa, Hallak, Moreira, & Guimarães, 2006). Across several studies, CBD demonstrated the same effectiveness in reducing psychotic-like symptoms in rodents, compared to a typical antipsychotic (haloperidol) and an atypical antipsychotic (clozapine; Moreira & Guimarães, 2005; Zuardi, Rodrigues, & Cunha, 1991; Gururajan, Taylor, & Malone, 2011). These effects were shown both within dopamine- and glutamate-based models, where CBD resembled atypical antipsychotic agents in that no extrapyramidal side effects were induced. CBD also proved capable of reversing THC-induced effects such as reduced social interaction (Malone, Jongejan, & Taylor, 2009) and apomorphine-induced sniffing, biting and stereotyped behavior in rats (Zuardi et al., 1991). Furthermore, in neurochemical studies CBD revealed similar neural activation patterns compared to atypical antipsychotics (Guimarães, Zuardi, Del Bel, & Guimarães, 2004). Taken together, preclinical data provide for support CBD's antipsychotic potential, suggesting a profile similar to that of atypical antipsychotic drugs.

Human experimental studies

Across multiple experimental models of psychosis, studies with healthy volunteers indicated antipsychotic-like properties of CBD. Research paradigms including binocular depth inversion and a mismatch negativity model suggested positive effects of CBD in attenuating psychotic-like symptoms and increasing cognitive performance (Leweke, Schneider, Radwan, Schmidt, & Emrich, 2000; Juckel, Roser, Nadulski, Stadelmann, & Gallinat, 2007). In addition, CBD attenuated psychotic-like effects in a glutamate-based model (Bosi, Hallak, Dursun, Deakin, & Zuardi, 2003). Finally, studies comparing the psychotomimetic effects of THC and CBD in humans revealed that CBD pretreatment (before THC admission) blocked the emergence of

psychotic symptoms, and posttreatment reduced THC induced effects, particularly anxiety (Bhattacharyya et al., 2010; Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982; Crippa, Zuardi, Martin-Santos, & Bhattacharyya, 2009).

Neuroimaging studies

Imaging studies also provide several clues of a potential antipsychotic effect of CBD. A series of functional imaging studies by Bhattacharyya and colleagues investigated brain activation patterns under THC and CBD in 15 healthy volunteers during tasks often impaired in psychosis (Bhattacharyya et al., 2009, 2010, 2012; Borgwardt et al., 2008; Fusar-Poli et al., 2009; Winton-Brown et al., 2011). THC and CBD were shown to have opposing effects on regional brain activation in areas associated with the pathophysiology of psychotic disorders, including the striatum, the prefrontal cortex and the medial temporal cortex. In a structural imaging study, Demirakca et al. (2011) found that CBD had a protective effect on cannabis use-associated gray matter volume reduction in the hippocampus. Hippocampal volume loss is a frequent finding in schizophrenia patients (Walker, Mittal, & Tessner, 2008); thus, a potential neuroprotective effect is a desirable feature of antipsychotic medication.

Epidemiological studies

Several epidemiological studies detected a relationship between psychosis or psychotic symptoms and THC/CBD concentration. Comparing cannabis use habits of first episode psychosis patients and healthy cannabis users revealed that patients were significantly more likely to have used high-potency cannabis, containing high THC and low CBD concentrations, for a longer duration and with higher frequency (Di Forti et al., 2009). Moreover, Morgan and colleagues showed that cannabis users who had a higher content of CBD in hair samples exhibited lower levels of positive symptoms such as delusions and hallucinations, suggesting

that the presence of CBD in the strain of cannabis consumed has a protective function against psychotic symptoms induced by THC (Morgan & Curran, 2008; Morgan et al., 2012). This finding was further replicated by Schubart et al. (2011). Hence, there are consistent findings that cannabis types which contain more CBD cause less psychotic-like experiences in the general population.

Tolerability

Safety and side effect studies of CBD were required before human administration (for a recent review see Bergamaschi, Queiroz, Zuardi, & Crippa, 2011). Extensive reports of CBD administration across a wide range of concentrations did not detect severe side effects or toxic effects in animal studies. In human studies, CBD did not induce side effects across a wide range of dosages including acute and chronic dose regimens, and it was shown that chronic CBD use with high doses up 1500 mg/kg a day were well tolerated. However, in vitro and in vivo studies showed potential drug metabolism interactions, cytotoxicity, and decreased receptor activity. The available data suggest that CBD can be safely administered over a wide dose range, but further double-blind, placebo-controlled trials are still needed to assess the effects of cannabidiol on biological systems.

Clinical studies

Clinical studies also attest to the antipsychotic efficacy of CBD. Zuardi and colleagues published several case studies and pilot studies demonstrating significant improvement of psychotic symptoms with CBD monotherapy in patients with psychotic symptoms (Zuardi et al., 1995, 2006, 2009, 2010). No adverse effects on motor functioning or cognition were detected. However, there were no, or only small improvements in treatment-refractory schizophrenia patients. To date, five randomized controlled trials (RCTs) and one open-label study investigating the acute

antipsychotic and potential procognitive effects of cannabidiol have been initiated, two of which have published data (see Leweke, Mueller, Lange, & Rohleder, 2016). The first double-blind, randomized controlled clinical trial compared treatment with CBD versus the atypical antipsychotic amisulpride in patients with acute paranoid schizophrenia or schizophreniform disorder (n=42) over a 4-week trial (Leweke et al., 2012). CBD and amisulpride displayed equal therapeutic efficacy in reducing psychotic symptoms; however, CBD treatment was accompanied by significantly fewer side effects (no prolactin increase, weight gain, or extrapyramidal symptoms). The same research group conducted a RCT in a double-blind cross-over design, comparing CBD versus placebo in 29 first-episode schizophrenic patients within a 4-week trial (University of Cologne, 2008). Results are currently pending publication.

A third RCT by Ranganathan et al. (Yale University, 2009) compared CBD and placebo over six weeks as an addition to a stable risperidone treatment (n=36), focusing on improvement of cognitive functioning. Results are yet to be published. A fourth double-blind RCT has recently been completed comparing effects of CBD versus placebo in adjunction with antipsychotic medication in 88 patients with psychotic disorders (GW Research Ltd, 2013). While results have not been formally published yet, it was recently announced that CBD was consistently superior to placebo regarding psychopathology and showed a reassuring safety profile (GW Pharmaceuticals, 2015). Two more clinical trials are currently ongoing: a study by Leweke and colleagues, comparing CBD to olanzapine and a placebo (Central Institute of Mental Health, 2015), and an open-label, add-on trial investigating of CBD in patients with treatment-refractory psychotic disorders (King's College London, 2013). In sum, currently available data suggest that CBD may exert clinically relevant antipsychotic effects while displaying a superior side-effect profile compared to conventional medication. However, preliminary evidence is limited with no information on long-term efficacy and tolerability available yet.

DISCUSSION

In conclusion, the preclinical and clinical studies discussed in this review provide promising initial support for CBD as an effective and safe antipsychotic compound. Preliminary evidence points to high tolerability, superior cost-effectiveness and a promising side effect profile, suggesting an attractive alternative to current antipsychotic treatment. However, the vast majority of current evidence stems from experimental non-clinical studies, with only limited clinical data available. Some clinical trials are currently ongoing and some studies remain to be published, but the duration of treatment is limited to six weeks of treatment at maximum and sample sizes are not sufficient to warrant conclusions. As suggested by Leweke et al. (2016), large-scale, randomized clinical trials both in the acute treatment as well as in the maintenance phase, for six months or longer are required to prove the safety and efficacy of cannabidiol in schizophrenia. Further, should this novel treatment option be introduced into clinical practice, careful monitoring of CBD use in humans is warranted, given the above-mentioned side effects that were found in some studies.

Interest in the endocannabinoid system has immensely increased over the years, as it may play a role in several disorders, including a variety of psychiatric conditions (for a recent review see Lutz, Marsicano, Maldonado, & Hillard, 2015). The last decade has shown a notable increase in scientific literature on CBD, owing to the identification of its anti-inflammatory and neuroprotective effects. Not only has it evolved as a new target for treatment approaches to schizophrenia, but other potential therapeutic applications of CBD may include anxiety and mood disorders (Crippa, Zuardi, & Hallak, 2010), as well as epilepsy (Dravet's syndrome) and other neurological disorders (Project CBD, 2015). Given the significant favorable evidence pointing to the therapeutic potential of cannabidiol in psychotic and other conditions, substantially more clinical work can undoubtedly be expected to follow.

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