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Review article

A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia

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ABSTRACT

Background and objectives: Cognitive impairment is a core symptom domain of schizophrenia, neurological disorders and substance abuse. It is characterised by deficits in learning, memory, attention and executive functioning and can severely impact daily living. Antipsychotic drugs prescribed to treat schizophrenia provide limited cognitive benefits and novel therapeutic targets are required. Cannabidiol (CBD), a component of the cannabis plant, has anti-inflammatory and antipsychotic-like properties; however, its ability to improve cognitive impairment has not been thoroughly explored. The aim of this systematic review was to evaluate preclinical and clinical literature on the effects of CBD in cognitive domains relevant to schizophrenia.

Methods: A systematic literature search was performed across numerous electronic databases for English language articles (January 1990–March 2016), with 27 articles (18 preclinical and 9 clinical studies) included in the present review.

Results: CBD improves cognition in multiple preclinical models of cognitive impairment, including models of neuropsychiatric (schizophrenia), neurodegenerative (Alzheimer's disease), neuro-inflammatory (meningitis, sepsis and cerebral malaria) and neurological disorders (hepatic encephalopathy and brain ischemia). To date, there is one clinical investigation into the effects of CBD on cognition in schizophrenia patients, with negative results for the Stroop test. CBD attenuates Δ^9-THC-induced cognitive deficits.

Conclusions: The efficacy of CBD to improve cognition in schizophrenia cannot be elucidated due to lack of clinical evidence; however, given the ability of CBD to restore cognition in multiple studies of impairment, further investigation into its efficacy in schizophrenia is warranted. Potential mechanisms underlying the efficacy of CBD to improve cognition are discussed.

Contents

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1. Introduction

Since the introduction of 'third generation' atypical antipsychotics in the 1990s, there have been relatively few clinically significant advances in treatment options for patients suffering from affective and non-affective psychotic disorders such as schizophrenia and bipolar disorder (Schubart et al., 2014). Antipsychotics have therapeutic efficacy in treating some of the positive (hallucinations, delusions) and negative (anhedonia, apathy) symptoms of schizophrenia; however, they are limited in their ability to treat the cognitive domain of the disease (Gray and Roth, 2007). Cognitive impairment is a core symptom underlying many neuropsychiatric disorders. Approximately 75–85% of people with schizophrenia experience deficits in cognition that negatively impact day-to-day living, including the ability to maintain employment, relationships and self-care (Barch and Ceaser, 2012). Cognitive deficits often precede the emergence of other symptoms in schizophrenia, are associated with poor medication compliance and a higher tendency for relapse in first episode psychosis (Meyer et al., 2011). In fact, cognitive deficits are considered a better prognostic indicator in schizophrenia patients than other symptom domains because the severity of cognitive dysfunction correlates with earlier disease onset (Gray and Roth, 2007) and can predict clinical course and future functional outcomes (Green, 2006). As current antipsychotic medications show minimal benefits for cognitive impairment (Gray and Roth, 2007) and have adverse side-effects (such as weight gain and motor disturbances) (Weston-Green et al., 2013), there is an urgent requirement to identify new pharmacological treatments that can enhance cognitive function and improve the overall quality of life for people with schizophrenia. In an effort to address cognitive dysfunction in schizophrenia, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative was developed that identifies 7 primary cognitive domains as targets for treatment in schizophrenia (Gray and Roth, 2007). These domains include processing speed, verbal learning and memory, attention and vigilance, reasoning and problem solving, visual learning and memory, social cognition and working memory (Gray and Roth, 2007). The authors (Gray and Roth, 2007) recommend that preclinical studies assessing the efficacy and functional outcomes of new pharmacological treatments in schizophrenia models should use behavioural tests that examine domains identified in MATRICS. Likewise, the MATRICS Consensus Cognitive Battery (a battery of 10 tests that examine the MATRICS cognitive domains) should be used in clinical trials that assess the efficacy of potential cognitive-enhancing drugs for schizophrenia, to ensure standardised testing and maximise reproducibility between trials (Gray and Roth, 2007).

Cannabis sativa is the most widely used drug in the world and contains over 70 different constituents, including delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) (Bossong et al., 2014). Compared to the general population, individuals with schizophrenia are twice as likely to consume cannabis, with evidence of worsened psychotic symptoms and a higher incidence of relapse and poor treatment outcomes in users (Bossong et al., 2014). Cannabis use during adolescence is a well-documented risk factor for developing schizophrenia and lowers the age of symptom onset (De Hert et al., 2011). Cannabis interacts with the endogenous cannabinoid system and alterations in endogenous cannabinoid signalling have been observed in patients with schizophrenia. For example, studies report elevated levels of the endogenous cannabinoids anandamide (AEA) and 2-arachidonyl glycerol (2-AG) in cerebrospinal fluid and blood samples of patients (De Marchi et al., 2003; Giuffrida et al., 2004; Leweke et al., 2007, 1999, 2012), while post-mortem brain tissue and neuroimaging studies report elevations in cannabinoid CB1 receptor density in brain regions implicated in cognition, in people with schizophrenia (Newell et al., 2006; Wong et al., 2010; Zavitsanou et al., 2004). Interestingly, Δ^9-THC administration induces symptoms in healthy volunteers that resemble psychosis, including hallucinations, delusions, depersonalisation and emotional lability, coupled with cognitive impairment in learning and memory domains (Bossong et al., 2014). On the other hand, initial observations in the 1970s suggested that the cannabis constituent CBD interferes with the detrimental actions of Δ^9-THC in terms of psychotic proneness and cognitive dysfunction (Perez-Reyes et al., 1973). Indeed, more recent studies have identified an inverse relationship between CBD content in cannabis strains and the prevalence of psychotic symptoms, such as hallucinations and delusions, suggesting a possible protective effect of CBD (Morgan and Curran, 2008; Schubart et al., 2011). Furthermore, clinical and preclinical studies spanning more than a decade (Gururajan et al., 2012; Leweke et al., 2012; Long et al., 2006; Moreira and Guimarães, 2005; Zuardi et al., 1991), demonstrate potential for CBD as an antipsychotic agent against the positive and negative symptoms of schizophrenia (as reviewed in (Iseger and Bossong, 2015)). Despite these findings, evidence of the efficacy of CBD to improve cognitive deficits associated with schizophrenia