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Cannabidiol, cognition and schizophrenia: a narrative review

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Abstract

Schizophrenia is a serious mental disorder affecting about 1% of the population. It is characterised by multiple symptoms which are mostly responsive to treatment with antipsychotic medications. Cognitive impairment is regarded as a core feature of illness which is mostly poorly responsive to treatment with the current antipsychotic medications. Improving cognitive function is an important treatment goal as it is associated with better outcomes in employment and quality of life. Adjunctive pharmacological treatments have been examined to improve measures of cognition but with limited success. Cannabidiol (CBD), has shown promise in preclinical models of cognitive deficits of schizophrenia. On the other hand, limited studies in small groups of patients with schizophrenia have shown no significant clinical benefits for cognitive function as an adjunct to ongoing treatment with antipsychotics. A single trial, in which CBD as a standalone treatment was compared to the antipsychotic medication amisulpride, showed significant changes in cognitive measures for both agents, with no statistically significant difference between them. It might therefore be concluded that the preclinical findings have failed to translate to the clinic. However, the preclinical findings themselves are based on a circumscribed set of studies in multiple cognitive models and have used varying doses and routes of drug administration. The same general methodological issues are present in the suite of clinical studies. Issues such as patient heterogeneity in terms of illness duration, formulation and dose of CBD employed, and length of cannabinoid treatment might militate positive findings. The limited clinical database available makes the benefits (or lack thereof) of CBD for the cognitive effects of schizophrenia uncertain. Continued research in much larger patient populations than have so far been investigated as well as a consideration of dose ranging studies are required to fully assess the potential risks against the benefits of CBD treatment for cognitive deficits in schizophrenia.

Keywords

Schizophrenia, cannabidiol, cognition, clinical trials, preclinical studies

Introduction

Schizophrenia is a syndrome with features which can include delusions, thought disorder and hallucinations, the so-called positive symptoms of the disorder [1]. Other features of the disorder include

the negative symptoms, such as apathy, lack of drive, slowness, and social withdrawal [2]. In addition, cognitive symptoms also form part of the syndrome [3]. In acute episodes of the disorder positive symptoms are likely to be most prominent, while the chronic syndrome is more likely to have a preponderance of negative and cognitive symptoms. In schizophrenia, prodromal signs and symptoms often appear before the emergence of the "full-blown syndrome" of the disorder and may be part of an evolving process of the disease. Symptoms may present months or years before the first hospitalization. Indeed, the diagnosis of schizophrenia, at least under the Diagnostic and Statistical Manual of the American Psychiatric Association [*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)] criteria, requires the "continuous signs of disturbance for at least six months. This six-month period must include at least one month of symptoms" [4]. The lifetime prevalence for schizophrenia is estimated at about 1.0% of the population although there are regional differences in prevalence rates [1].

Cognitive deficits are regarded as a core feature of the illness and include deficits in attention and attentional performance, problem-solving abilities, memory (including spatial and verbal), and executive/frontal function [3]. These cognitive deficits are often present early in the illness and may vary little with the progress of the disorder, although in some cases there is progressive deterioration. The deficits have been linked to poor functional outcome and to future unemployment [5]. Both positive and negative symptoms can improve but the cognitive deficits often remain despite the improvement in other dimensions of the disorder. In the past it was thought that such cognitive symptoms were the result of side effects of the medications used to treat the disorder. While it is certainly true that antipsychotic medications, as well as some medications used to treat their side effects, do affect cognitive performance in both patients and healthy control subjects, it is now generally accepted that impairment of cognitive function is part of the disorder and not simply an effect of medication.

Schizophrenia is widely considered as a neurodevelopmental disorder, i.e., there has been a combination of adverse events in the prenatal or perinatal life which leads to development of the disorder. The current models of the aetiology of schizophrenia suggest a combination of genetic and environmental factors which result in the impairment of brain development throughout both the prenatal and postnatal period leading to the disorder. It is likely that cognitive deficits occur within this complex matrix of neurodevelopment [6, 7].

The precise cause of the cognitive deficits in schizophrenia is unclear. Schizophrenia is widely considered a polygenic disorder, with small contributions from multiple genes adding to the risk for the disorder [8]. Furthermore, environmental factors such as obstetric complications, and poor socioeconomic circumstances, among others also seem to contribute to risk [8]. As cognitive deficits form part of the syndrome, these gene-environment interactions likely contribute to the manifest cognitive abnormalities. At the neuropathological level, various aetiologies have been proposed including a disturbed balance between excitatory microcircuits and inhibitory microcircuits in the central nervous system [8]. Such a proposal posits the involvement of multiple neurotransmitter systems including dopamine, γ aminobutyric acid (GABA), glutamate, and acetylcholine interacting with one another. Given this interplay between neurotransmitter systems, it is not surprising that most attempts to improve cognitive function in schizophrenia have focussed on the use of pharmacological agents which alter activity within these systems. Most pharmacological manipulations have met with limited success. Non-pharmacological approaches have also been tried where a small effect on working memory has been observed from transcranial magnetic stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) [9].

Despite the fact that antipsychotic medications are effective for the treatment of the positive symptoms of the disorder, the negative and cognitive symptoms have been proven to be more stubborn to pharmacological interventions [8]. Given the relationship between impaired cognition and functional outcomes for patients, recent strategies have focussed on interventions that might boost cognitive performance. Pharmacological adjuncts have been at the forefront of these endeavours with the potential of cannabidiol (CBD) oil among the substances investigated incorporating both preclinical and clinical assessments.

Search strategy

The author searched the PubMed database (National Library of Medicine) and the Web of Science (Clarivate Analytics PLC) using the terms Schizophrenia, Cognition, Cannabidiol. A database of 85 references were returned from PubMed (a similar overlapping number of references was returned from Web of Science) and each abstract was reviewed by the author. Articles on 'social cognition' were manually excluded as were articles reviewing cognition in schizophrenia in general which did not specifically include cannabidiol in the abstract. Both preclinical and clinical studies were retained. From the 'final' set of articles obtained, the reference lists were screened manually for any additional references not included in the two overlapping searches.

CBD

Plants from the family *Cannabaceae* include the species *Cannabis sativa* and *Cannabis indica* which consist of hundreds of different chemical compounds including more than a hundred different cannabinoids [10]. Most cannabinoids are present in trace amounts, but the most common cannabinoids are Δ^9-tetrahydrocannabinol (THC) and CBD. Depending on the cultivation conditions, the content of THC and CBD can vary while hybrid strains have been developed to increase THC content [10]. From a psychopharmacological perspective, THC has psychoactive effects whereas CBD is not active [11]. This later substance has attracted interest because of its putative therapeutic role in multiple disorders [10–12], but most notably in epilepsy, particularly Dravet and Lennox-Gastaut syndromes [13]. CBD has been shown to interact with numerous target receptors in both the central and peripheral nervous system [14]. Of note, the compound does not bind to the orthostatic site for cannabinoid-1 (CB_1) and CB_2 receptors, but rather binds to the allosteric sites [15]. CBD binds as an inverse agonist/antagonist at the CB_1 site and as an antagonist at the CB_2 site. In contrast, actions at transient receptor potential vanilloid (TRPV; particularly TRPV-1 receptors) channels and Serotonin 1A ($5\text{-}HT_{1A}$) receptors (agonist actions) are partially responsible for the pharmacodynamic effects of CBD [14]. Indirect effects on endocannabinoid signalling, such as modulating the concentrations of the endocannabinoid ligand anandamide may also be important as a mediator of the effects of CBD [16]. CBD has been shown to act as a partial agonist at dopamine D_2 (high affinity site) receptors [17]. This action is like that of the antipsychotic agents aripiprazole and brexpiprazole, an effect which is putatively important for treating the negative and cognitive symptoms of schizophrenia. Further research is necessary to elucidate the mechanisms responsible for the actions of CBD. While given the multiple identified molecular interactions of the drug, it seems that the multiplicity of putative therapeutic effects is dependent on many different targets.

Effect of CBD on cognitive function

Preclinical studies

Animal paradigms, which mirror some symptoms observed in patients with schizophrenia, have been used to identify potential treatment modalities for the disorder. Models which induce symptoms have been categorised as falling into one of four different modalities: developmental, drug-induced, lesion or genetic manipulation, which have been reviewed elsewhere [18]. While most of the models successfully mirror positive symptoms of the disorder, the reflection of negative symptoms and cognitive deficits have been proven more elusive. Nevertheless, cognitive deficits are present in some animal models among the different symptom induction modalities and have been utilised to evaluate the potential of CBD as a treatment. The relevant studies are summarised in Table 1.

Drug induced models

Cognitive impairment in schizophrenia has been associated with abnormalities of glutamatergic transmission through *N*-methyl-*D*-aspartate (NMDA)-type receptors [19]. Thus, memory deficits can be induced in animals by administration of NMDA antagonists such as ketamine and phencyclidine (PCP), which offers a paradigm to examine the effects of treatment modalities on cognitive function. In a group of

Table 1. Activity of CBD in preclinical cognitive models

Species	Model system	Dose of CBD	Memory test	Outcome	Reference
C57BL/6J mice	MK-801	30 mg/kg, 60 mg/kg	NORT	Effects in the NORT attenuated by CBD	[22]
Sprague Dawley rats	In utero exposure to poly(I:C)	30 mg/kg	NORT, alternating T-maze	CBD improved performance	[26]
Male Wistar rats	Chronic methamphetamine exposure	32 nmol i.c.v., 160 nmol i.c.v.	Y-maze, NORT	CBD improved performance	[23]
Male Sprague-Dawley rats	Repeated ketamine exposure	Acute doses: 1.875 mg/kg to 30 mg/kg; chronic doses: 7.5 mg/kg twice daily	NORT	CBD improved memory function	[20]
Male Swiss mice	MK-801	1 mg/kg, 5 mg/kg, 30 mg/kg	Passive avoidance	CBD improved all aspects of fear memory	[19]
Male *NRG1* mice	Genetic model	30 mg/kg	Fear conditioning	No effect CBD on fear conditioning	[30]
Female Sprague-Dawley rats	In utero exposure to MAM	10 mg/kg, 30 mg/kg per day i.p.	NORT	Reduction in DI partially reversed by 30 mg/kg CBD	[27]
Female Sprague-Dawley rats	In utero exposure to THC	30 mg/kg per day	NORT	Reduction in DI reversed	[28]

DI: discrimination index; i.c.v.: intracerebroventricularly; MAM: methylazoxymethanol acetate; MK-801: dizocilpine; NORT: novel object recognition task; *NRG1*: neuregulin-1; poly(I:C): polyinosinic:polycytidilic acid; i.p.: intraperitoneally

male Sprague-Dawley rats, daily injections (i.p.) of ketamine 30 mg/kg for 10 days produced cognitive dysfunction as determined by the NORT [20]. The NORT assesses working memory function [21]. Following a washout period of 6 days, the effects of CBD were assessed after an acute dose and repeated doses. The discrimination index in the NORT (a ratio of time spent examining the novel object compared to the familiar object) increased statistically significantly after an acute dose of CBD in a dose dependent manner. Both 7.5 mg/kg and 30 mg/kg were effective but 1.875 mg/kg, 3.75 mg/kg, and 15 mg/kg were not. Treatment for 6 days (7.5 mg/kg twice a day, pure CBD) was also effective in returning the discrimination index to its baseline level. CBD itself had some pro-cognitive activity.

Another NMDA receptor antagonist MK-801 has been used to induce memory impairment in rodents and the effects of CBD to reverse the deficits were evaluated in two independent studies (Table 1). Male C57BL/6J mice, aged 6 weeks at the start of the study, were treated with 1mg/kg MK-801 for 28 days [22]. Commencing the sixth day of the MK-801 treatment, CBD (30 mg/kg and 60 mg/kg) or clozapine (1 mg/kg) was administered and continued until day 28 of the study (end of the MK-801 administration). The effect on cognitive function was assessed using the NORT on day 30. Both doses of CBD as well as clozapine were able to attenuate the effects of MK-801 in the NORT. There was no effect of these doses on tests of anxiety (elevated plus maze, open field), suggesting that the observed increase in exploration of the novel object in the NORT test was not due to an anxiolytic effect of the agents. In the acquisition trial, neither CBD (both doses) nor clozapine affected the behaviour of the animals, attesting to the lack of effect of the drugs on place preference.

Memory impairments were induced in male Swiss mice (4 weeks old) by an injection (i.p.) of MK-801 (0.6 mg/kg) and the effectiveness of CBD to reverse various aspects of fear learning was assessed using the passive avoidance test [19]. Doses of CBD ranging from 1 to 30 mg/kg were administered i.p. The highest dose of CBD improved all phases of fear memory whereas the lower doses (1 mg/kg and 5 mg/kg) were effective in the consolidation and retrieval phases, but not the acquisition phase.

Chronic exposure to methamphetamine [2 mg/kg, subcutaneously (s.c.), twice daily for 10 days] was used to induce memory performance deficits in male Wistar rats [23]. At the end of a 10-day abstinence period, the animals were tested in the Y-maze and the NORT was used to determine the cognitive function. During the abstinence period, CBD (32 nmol and 160 nmol) was administered i.c.v. As is shown by the

tendency of the rats to enter previously unexplored arms of the Y-maze, CBD improved the spatial memory. Similarly, short-term memory was improved by both doses of CBD in the NORT, but long-term memory in this apparatus was only improved by the higher dose of CBD. Given the route of the administration of CBD (i.c.v.), this might reflect the diffusion of the drug away from the site of action or clearance from the brain that an effective concentration is not maintained.

In utero exposure models

Administration of the synthetic double-stranded RNA virus [poly(I:C)] to pregnant dams at gestational day 15 produces cytokine activation in the resultant offspring and a schizophrenia-like phenotype [24]. Specifically, maternal poly(I:C) has been shown to alter nonspatial information processing as assessed by the NORT [25]. Thus, the model has been used to examine the ability of CBD to attenuate cognitive deficits similar to those observed in patients with schizophrenia. Following 3 weeks of treatment with CBD (10 mg/kg), male offsprings were tested in the NORT and alternating T-maze, a measure of working memory [26]. CBD was associated with an improvement in the performance in both tests.

Prenatal exposure of pregnant Sprague-Dawley rats to the antimitotic agent MAM at gestational day 17 produced offspring with long-lasting deficits seen in other animal paradigms used in schizophrenia research [27]. Pertinent to the current discussion, a reduction in the discrimination index of the NORT was observed. Daily treatment with CBD (10 mg/kg or 30 mg/kg) through the postnatal period days 19 to 39 resulted in a reversal of the deficit (30 mg/kg only was statistically significant). In contrast, the antipsychotic drug, haloperidol (0.6 mg/kg per day), and the CB_1 receptor antagonist/inverse agonist AM251 (0.5 mg/kg per day) did not result in reversal of the cognitive deficit. The data suggest preservation of cognitive ability by CBD provided intervention is in an early phase of the disorder.

In a similar experiment, perinatal exposure to Δ^9-THC in female Sprague-Dawley rats from gestational day 15 to postnatal day 9 resulted in behavioural and molecular changes of adult offspring [28]. Specifically at the molecular level, cannabinoid (CB_1) and dopamine D_2 receptors were increased and the methylation status of the D_2 regulatory region was reduced. Furthermore, recognition memory, as measured by the discrimination index in the NORT, was reduced by perinatal exposure to THC. Treatment of the offspring with CBD (30 mg/kg per day) from postnatal day 19 to day 39 reversed the discrimination index findings in adulthood (i.e., postnatal day 100). The data align with the notion that early intervention can preserve cognitive function as is noted in the study with MAM.

Genetic models

Although the cause(s) of schizophrenia is not known, it is well recognised that genetic abnormalities play a role. One such susceptibility gene, the neuregulin gene (*NRG1*), has been associated with schizophrenia in genome wide studies [28]. The *NRG1* transmembrane domain heterozygous (TM HET) mutant mouse exhibits a phenotype which is consistent with that found in schizophrenia, including cognitive alterations [29]. Adolescent mutant male rats were compared in tests of locomotion, social behaviour, sensorimotor gating, and cognition to their wild type controls following 7 weeks of daily intraperitoneal injection of 30 mg/kg CBD [30]. CBD failed to prevent any of the schizophrenia-like deficits in these animals, including fear-associated learning and memory.

These studies in animal models of schizophrenia-like cognitive deficits are generally consistent in showing that CBD administration can ameliorate the associated behaviours. Although there are some exceptions, these may be related to the type of model employed in the study. Pharmacological models tend to be focussed on the NMDA or dopamine receptor and are limited in their validity. On the other hand, the neuregulin model is claimed to have face, construct, and predictive validity for schizophrenia, yet CBD does not appear to be active in that model. In terms of cognitive function, evaluative tests also have limitations. Clearly human trials are the *sine qua non* for determining activity against the cognitive deficits of schizophrenia.

Human studies

Healthy volunteers

Few studies have examined the cognitive enhancing properties of CBD taken alone in healthy subjects. On the other hand, the ability of CBD to block the effects of THC on cognition has been studied as well as the cognitive effects in patients with neurological conditions [31]. While some studies suggested that CBD was able to counteract the effects of THC on cognitive function in healthy subjects [32, 33], this finding has not been universal with either further impairment of performance [34] or no effects at all [35]. The differences may be related to methodological issues such as the dose and route of administration of THC chosen (oromucosal spray, vaping, or tablet).

A double-blind, placebo-controlled, randomised, cross-over trial, examined the effect of CBD on cognitive function in healthy, young volunteers [36]. CBD was administered as a vaping liquid (12.5 mg; vaping) and cognitive function was assessed using a verbal learning task to measure delayed free recall and two pictorial n-back tasks with increasing cognitive load. CBD enhanced verbal episodic memory as measured by the verbal learning task but yielded no change in attention or working memory performance as measured by the two pictorial n-back tasks. Clearly, further evaluation of CBD in healthy volunteers, for example, under some form of cognitive load, would aid in assessing the value of the substance as a cognitive enhancer.

Patients with schizophrenia

Based on the studies in preclinical models and in healthy volunteers, several studies have been performed in patients with schizophrenia to evaluate potential beneficial effects of CBD on cognitive function (Table 2). In a group of 28 medicated patients with schizophrenia, the effect of two different doses of CBD administered in gelatin capsules was compared to placebo on performance in the Stroop Colour Word Test (SCWT) [37]. Compared to a baseline session conducted one month beforehand, all three groups of patients had an improved performance on the test. Thus, an acute dose of CBD did not appear to offer any significant cognitive benefits over placebo.

Table 2. Effects of CBD on cognitive function in patients with schizophrenia

Subjects; diagnosis	Study design	Dose of CBD; formulation	Measure of cognition	Cognitive outcome	Reference
18 M, 10 F (> 18 years); DSM-IV schizophrenia	Randomised, double-blind, placebo-controlled, parallel group	300 mg, 600 mg; gelatin capsules; matching placebo	SCWT	No beneficial effects of CBD as single dose	[37]
51 M, 37 F (mean age 40.8 years); DSM-IV schizophrenia	Double-blind, placebo-controlled, parallel group	1000 mg/day for 6 weeks; oral solution	BACS	BACS improved not significantly	[38]
25 M, 11 F (18–65 years); DSM-IV schizophrenia or schizoaffective disorder	Double-blind, placebo-controlled, parallel group	600 mg/day for 6 weeks; oral tablet	MATRICS	No significant effects on cognition	[39]
32 M, 7 F (18–50 years); DSM-IV schizophrenia or schizophreniform psychosis	Double-blind, randomised, parallel group	Up to 800 mg/day for 4 weeks; oral tablet	Measures of pattern recognition, attention, working memory, verbal and visual memory, learning, processing speed, and verbal executive functions	No difference between CBD-treated and AMI-treated patients; improved function for visual memory, processing speed, sustained attention, and visuomotor coordination	[41]

AMI: amisulpride; BACS: Brief Assessment of Cognition in Schizophrenia; MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia; F: female; M: male

The efficacy of CBD as an adjunct to the existing antipsychotic medication (mostly aripiprazole, olanzapine, risperidone) was assessed in a double-blind, placebo-controlled trial in patients meeting DSM-IV criteria for schizophrenia [38]. Patients had previously demonstrated at least a partial response to antipsychotic medication, i.e., they were not treatment resistant. Subjects were randomly allocated to either CBD (1,000 mg/day; 10 mL of a 100 mg/mL oral solution) or matching placebo for 6 weeks. In addition to measures of clinical response, cognitive performance was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline days 8, 22 and 43 of treatment. A greater improvement in the BACS composite score was observed in the CBD group than in the placebo-treated patients, but the difference was not statistically significant. Post-hoc analysis of BACS domains showed a significantly greater improvement in motor speed in the CBD group relative to placebo, and a non-significant greater improvement in executive function. The study is perhaps limited by the short duration of treatment, the lack of a dose ranging study for CBD and the use of a single cognitive test.

In a similar double-blind, randomised, placebo-controlled study, the effect of CBD (300 mg twice daily) was compared to placebo in patients with chronic schizophrenia [DSM-IV-Text Revision (TR) diagnostic criteria] who were stabilised on various antipsychotic medications [39]. Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) while cognitive symptoms were assessed with the MATRICS Consensus Cognitive Battery (MCCB). Psychopathology scores improved significantly across the treatment period for both groups with no significant differences between CBD and placebo. In terms of cognitive effects, while placebo-treated patients showed improvement over time, there was no effect of CBD on composite MCCB scores or for any of the subtests of the battery. There was a higher use of the first-generation antipsychotic medications in the CBD group than for the placebo-treated patients. These agents are known to possess significant anticholinergic effects which can affect cognitive performance [40].

The efficacy of CBD (up to 800 mg/day) as a monotherapy for acute paranoid patients with schizophrenia was compared to amisulpride (up to 800 mg/day) in a double-blind, randomised, parallel-group trial conducted over 4 weeks [41]. Neurocognitive performance was a secondary outcome of the study and assessed cognitive outcomes in the domains: pattern recognition, attention, working memory, verbal and visual memory and learning, processing speed, and verbal executive functions using a battery of validated standardised tests with test-retest reliability. Psychopathology scores were assessed at baseline, weeks 2 and 4 of treatment and showed that there was no statistically significant difference between treatments. Patients in both groups had significant improvement in the total PANSS scores as well as the positive, negative, and general subscales. Compared to the baseline assessment, patients in both treatment groups improved on neuropsychological domains after 4 weeks of treatment. There were no statistically significant differences between groups with respect to neuropsychological tests.

For the CBD-treated patients, statistically significant improvements were noted for sustained attention, visual memory, processing speed, and visuomotor coordination with small to modest effect sizes in each. There did not appear to be any relationship between improved cognitive performance and improved psychopathology, suggesting that deficits in the cognitive domain arise as part of the syndrome of schizophrenia, not consequently. A significant difference between this and the previous studies is that patients were treated with CBD as a monotherapy not as an adjunct to the existing drug regimens. Whether this accounts for differences in outcomes from a cognitive perspective requires further and more extensive evaluation.

Conclusions

Although preclinical studies suggest a potential for the use of CBD as a cognitive enhancer, there are clear limitations of the models used in that they are unable to reproduce the full syndrome of schizophrenia. Interactions between neural circuits are, in all probability, important for developing symptoms of the disorder, including the cognitive deficits [42]. Pharmacological models are based on alterations affecting selective receptor subtypes and limited neural pathways. Translation from the preclinical to the clinical has not resulted in comparable effects on cognition. Several factors may have influenced the negative findings with CBD in the studies conducted to date. Although most clinical studies have used well validated tests of

cognitive function, few have addressed the use of CBD alone as a cognitive enhancing agent. In short-term administration (4 weeks), CBD appeared to possess both antipsychotic efficacy as well as cognitive enhancing properties in a group of patients with an acute episode of illness [41]. On the other hand, no differences were observed in patients treated with a standard antipsychotic agent leaving the question of cognitive enhancement unresolved [39]. Furthermore, the length of treatment was short compared to the chronic nature of the disorder. When used an adjunctive treatment to antipsychotic agents, CBD also failed to provide any evidence of significant improvement in cognitive function [38]. In this situation, the negative effects of medications on cognition need to be taken into consideration. Clinical studies conducted so far have had small samples with consequently low statistical power to detect small effect sizes, which are more likely to occur.

If it is assumed that cognitive deficits in schizophrenia worsen over time, as part of an ongoing neurodegenerative process of the disorder, then it can be assumed that better effects on cognition are likely in patients with shorter durations of illness. This hypothesis has not been tested in studies to date. However, some preclinical studies reviewed here suggest that earlier intervention with CBD may preserve cognitive function [27, 28], making phytocannabinoids an important potential therapeutic target, especially in adolescent onset of the disorder [43]. CBD may induce epigenetic modifications of several target genes [44] which have been suggested as potential targets for treating the cognitive deficits, a common hallmark in several psychopathologies including schizophrenia. Further research is also necessary to define the doses of CBD which might improve cognitive function. Various doses have been used in both preclinical and clinical studies with little attempt in the clinical domain to undertake a dose-response trial. This coupled with the small sample sizes in studies suggests that a more extensive database is necessary to evaluate any potential recommendations for the use of CBD as a cognitive enhancer in schizophrenia.

Abbreviations

BACS: Brief Assessment of Cognition in Schizophrenia

CB_1: cannabinoid-1

CBD: cannabidiol

DSM-5: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*

i.c.v.: intracerebroventricularly

MAM: methylazoxymethanol acetate

MK-801: dizocilpine

NMDA: *N*-methyl-*D*-aspartate

NORT: novel object recognition task

NRG1: neuregulin-1

poly(I:C): polyinosinic:polycytidilic acid

THC: tetrahydrocannabinol

Declarations

Author contributions

TRN: Conceptualization, Investigation, Writing—original draft, Writing—review & editing.

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The author declares he has no conflicts of interest.

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