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Review

Cannabidiol as a potential treatment for psychosis

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***Abstract*:** Psychotic disorders such as schizophrenia are heterogeneous and often debilitating conditions that contribute substantially to the global burden of disease. The introduction of dopamine D2 receptor antagonists in the 1950s revolutionised the treatment of psychotic disorders and they remain the mainstay of our treatment arsenal for psychosis. However, traditional antipsychotics are associated with a number of side effects and a significant proportion of patients do not achieve an adequate remission of symptoms. There is therefore a need for novel interventions, particularly those with a non-D2 antagonist mechanism of action. Cannabidiol (CBD), a non-intoxicating constituent of the cannabis plant, has emerged as a potential novel class of antipsychotic with a unique mechanism of action. In this review, we set out the prospects of CBD as a potential novel treatment for psychotic disorders. We first review the evidence from the perspective of preclinical work and human experimental and neuroimaging studies. We then synthesise the current evidence regarding the clinical efficacy of CBD in terms of positive, negative and cognitive symptoms, safety and tolerability, and potential mechanisms by which CBD may have antipsychotic effects.

Keywords: antipsychotics, cannabidiol, cannabinoids, cannabis, psychosis, schizophrenia, treatment

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Introduction

Psychotic disorders such as schizophrenia are heterogeneous and often debilitating conditions that contribute substantially to the global burden of disease.[1] Patients with psychosis present with a range of psychopathology across positive, negative and cognitive symptom domains. The introduction of dopamine (primarily D2) receptor antagonists in the 1950s revolutionised the treatment of psychotic disorders and they remain the mainstay of our treatment arsenal for psychosis.[2] However, a significant proportion of patients either do not respond to traditional antipsychotics or do not achieve a complete or adequate remission of symptoms.[3] In addition, most current antipsychotics only target the positive symptoms of psychosis, with little effect on negative or cognitive symptoms.[2] Dopamine-acting antipsychotics are also associated with a number of side effects,[4] some of which can be severe and which may contribute to nonadherence. There is therefore a need for novel interventions, particularly those with a non-D2 antagonist mechanism of action, and which may thereby avoid some of the adverse effects of modulating the dopamine system directly. In line with this, over recent years there has been increasing interest in the development of treatments with alternate mechanisms of action.[5]

Accumulating evidence implicates the endocannabinoid system in the pathophysiology of psychosis.[6,7] A recent meta-analysis concluded that patients with psychosis have significantly higher levels of the endocannabinoid anandamide both in cerebrospinal fluid and in blood, and higher expression of the main central cannabinoid 1 receptor (CB1) on peripheral immune cells.[8] This elevated endocannabinoid tone was observed at all stages of illness, from the prodrome to chronic psychosis.[8] Alterations in CB1 receptor expression have also been observed in postmortem tissue and *in vivo* in patients with psychosis.[9–11]

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If the endocannabinoid system plays a role in psychosis pathophysiology, it raises the interesting possibility that pharmacological compounds that modulate this system may have therapeutic value.

Cannabidiol (CBD), a phytocannabinoid constituent of *Cannabis sativa*, has been heralded as one such potential treatment. While the main psychoactive ingredient in cannabis, delta-9-tetrohydrocannabinol (THC), has anxiogenic, psychotomimetic and amnestic effects, CBD is non-intoxicating and has potential anxiolytic, antipsychotic and anticonvulsant properties, and no detrimental effects on memory.[12] Epidemiological findings support these opposing effect profiles; extensive evidence implicates cannabis use as a risk factor for the development of psychosis and poor outcomes in cannabis-using patients.[13,14–19] However, the adverse effects of cannabis use on the risk of onset and subsequent outcome in psychosis are particularly evident in those using high potency skunk-like cannabis (i.e. with high levels of THC and low levels of CBD) as opposed to those using hash-like cannabis (i.e. with lower THC and higher CBD).[15,20–22] This pattern of findings is consistent with evidence that CBD not only has opposing effects to THC but may also block some of its adverse (and particularly psychotomimetic) effects.[23,24]

Importantly, CBD has a different mechanism of action to dopamine receptor antagonists and could therefore represent a completely novel class of antipsychotic treatment.[25] This would be associated with numerous benefits. First, by avoiding dopamine receptor antagonism, adverse effects such as extrapyramidal symptoms and increased prolactin may be avoided. Second, if CBD acts *via* different molecular pathways to current antipsychotics, it could be used not only as monotherapy but potentially as an adjunctive treatment alongside existing antipsychotics, with potential complementary gains in efficacy. While CBD is currently being tested in relation to a number of psychiatric disorders and physical health conditions,[12] this review synthesises and summarises the current evidence regarding the therapeutic potential of CBD as a treatment for psychosis.

Evidence for antipsychotic potential of cannabidiol

The accumulating evidence regarding the antipsychotic potential of CBD has emerged from a number of different sources. This includes preclinical work, experimental studies in healthy human volunteers comparing the neurocognitive effects of THC and CBD as well as studies examining whether CBD can block or attenuate the symptomatic effects of THC.

Preclinical evidence

Indirect evidence for the antipsychotic and anxiolytic effects of CBD comes from preclinical studies, where specific features of psychotic disorders are modelled in animals and allow potential therapeutic effects to be examined from molecular to behavioural levels.[26]

Hyperlocomotion. Hyperlocomotion is thought to be a model of positive psychotic symptoms and can be rescued using antipsychotics.[26] CBD has been shown to reduce hyperlocomotion induced by amphetamine (dopamine agonist) and ketamine [N-methyl-D-aspartate (NMDA) receptor antagonist] while at the same time not inducing catalepsy,[27] which suggests that it has antipsychotic-like beneficial effects without the detrimental motor side effects, with a profile resembling that of the atypical antipsychotic clozapine.[28]

Pre-pulse inhibition deficits. Pre-pulse inhibition (PPI) deficits represent sensorimotor gating abnormalities, thought to be a stable trait (bio) marker that is present across the psychosis spectrum.[29] Peripubertal CBD has been found to prevent the development of PPI deficits in the spontaneously hypertensive rat strain model,[30] which suggests that CBD may have long-lasting prophylactic effects, while it did not negatively impact PPI in control mice.

Social withdrawal and cognition. Methylazoxymethanol treatment induces numerous behavioural and cognitive deficits (social interaction and novel object recognition) as well as a range of pathophysiological manifestations analogous to those in schizophrenia,[31] including altered CB1 expression in prefrontal cortex. Peripubertal CBD reversed the methylazoxymethanol-induced alterations in CB1 expression and the schizophrenia-like phenotype, neither of which are rescued by haloperidol.[32] CBD has been found to reduce social withdrawal induced by THC but not polyinosinic-polycytidylic acid.[33,34] CBD can also attenuate MK-801 (an NMDA receptor antagonist)-induced changes in social behaviours, cognition and expression of various glial markers.[35] These latter findings suggest potential neuroprotective and anti-inflammatory

properties of CBD,[12] which is supported by independent evidence that CBD can promote hippocampal neurogenesis and rescue memory function,[36,37] consistent with human studies showing that CBD attenuates THC-elicited cognitive impairment.[23,38]

Human experimental and neuroimaging studies

Complementary insight into the antipsychotic potential of CBD has come from neuroimaging studies, which provide a means to noninvasively examine the systems (i.e. neural substrates) on which CBD may act to produce its antipsychotic and anxiolytic effects *in vivo*.

THC and CBD have been shown to have opposite effects on regional brain activation across a variety of cognitive tasks in healthy individuals.[24] Interestingly, this has been found in brain regions where patients with psychosis show dysfunction and during tasks that are known to be impaired by cannabis use. Using a double-blind, placebo-controlled, repeated-measures design, 15 healthy volunteers were studied on three occasions with functional magnetic resonance imaging (fMRI) after receiving a single dose of CBD (600 mg), THC (10 mg) or placebo.[24] In this series of experiments, THC-induced psychotic symptoms were directly related to the attenuating effects of THC on striatal activation during verbal recall and salience processing,[24,39] suggesting that the psychotogenic effects of THC may be mediated in part by effects on the striatum. In contrast, CBD augmented activation in the same regions during the task and did not induce psychotic symptoms. When viewing fearful faces, THC augmented activation in the amygdala, which was associated with induction of anxiety symptoms and increased physiological anxiety (measured using skin conductance response).[24] Conversely, CBD attenuated amygdala activation and this was significantly associated with the concurrant CBD-induced decrease in physiological anxiety (skin conductance response), suggesting that these effects may account for the anxiolytic properties of CBD. THC and CBD also had directly opposing effects on activation in the hippocampus during response inhibition,[24] the superior temporal cortex when listening to speech,[24] the occipital cortex during visual processing and on functional connectivity within regions processing attentional salience.[24,40]

Further evidence for the protective effects of CBD against the psychotomimetic, anxiogenic, and cognition-impairing effects of THC comes from experimental studies where the two cannabinoids have been co-administered. THC can be used as an experimental model of psychosis in humans because its acute administration in healthy individuals can induce transient psychotic-like symptoms (including both positive and negative symptoms), as well as cognitive deficits resembling those seen in schizophrenia.[41–47] In one study, six healthy volunteers received intravenous THC (1.25 mg) on two occasions, once preceded by intravenous placebo and once by CBD (2.5 mg) in a double-blind, within-subject design.[24] At the group level, THC administration with placebo pretreatment was associated with transient psychotomimetic effects, which was not observed under the CBD pretreatment condition.[24] A larger between-group study ($n = 48$) showed that relative to placebo, pretreatment with 600 mg oral CBD reduced the paranoia and impairments in episodic memory elicited by 1.5 mg intravenous THC.[23]

In summary, a growing body of literature suggests that CBD attenuates the propsychotic, anxiety and cognitive effects elicited by THC in healthy individuals at both the neurophysiological and behavioural (psychopathological) level. In addition, CBD has opposite effects to THC on regional brain activation and functional connectivity across a range of cognitive tasks (including salience processing, learning and memory, response inhibition and fear processing) in regions known to be disrupted in patients with psychosis.[24,39,40] Together, this accumulating evidence supports a potential therapeutic role for CBD in the treatment of psychosis and is consistent with independent evidence that CBD has antipsychotic effects in patients with the disorder (see below).

Cannabidiol in psychosis: current clinical evidence

Positive and negative psychotic symptoms

Initial studies. The 1990s saw the first studies investigating the effects of CBD in patients with psychosis. Results from a single ($n = 1$) case study of a 19-year-old female with acutely exacerbated schizophrenia reported that oral CBD, titrated up to 1500 mg/day over 4 weeks, was associated with a reduction in psychotic symptoms as measured with the Brief Psychiatric Rating Scale (BPRS).[48] A subsequent case series examined the effects of

oral CBD monotherapy (up to 1280 mg/day) for 30 days in three patients with treatment-resistant schizophrenia.[49] Here, one patient showed mild improvement in BPRS scores while two did not, but CBD was well tolerated: there were no side effects reported even up to the maximum dosage.[49] CBD has now been investigated in a number of larger-scale studies including randomised controlled trials (Table 1). The current review was not intended to be a fully systematic review, but to our knowledge, the information regarding previous clinical trials of CBD in psychosis is a complete and accurate record of all relevant studies up to July 2019.

CBD as monotherapy. One of the first landmark studies in patients with schizophrenia compared up to 800 mg/day of oral CBD with up to 800 mg/day of the antipsychotic amisulpride. In a randomised, double-blind, parallel-arm trial, 39 patients with an acute exacerbation of schizophrenia symptoms were treated over 4 weeks.[53] By day 28, there was a significant reduction in positive symptoms, as measured using the Positive and Negative Syndrome Scale (PANSS), in both the CBD group (change from baseline to day 28; $M \pm SD = -9.0 \pm 6.1$, $p < 0.001$) and the amisulpride group (-8.4 ± 7.5, $p < 0.001$), with no significant difference in efficacy between the treatments.[53] This pattern of findings emerged also for negative, total and general symptoms, with significant reductions by day 28 in both treatment arms (all change-from-baseline comparisons $p < 0.001$), and no significant between-treatment differences. These findings were the first robust indication that CBD may have antipsychotic efficacy, given the suggestion of noninferiority to the D2/D3 antagonist amisulpride. However, the most striking findings came from the evaluation of side effects. Extrapyramidal symptoms, weight gain and increased prolactin are common side effects of antipsychotics[4]; amisulpride significantly increased each of these parameters from baseline to day 28 (all $p < 0.05$).[53] However, no significant change was found in any of these side effects in the CBD group, and the between-treatment difference was significant (all $p < 0.01$), with CBD demonstrating a markedly superior side-effect profile.[53] The finding of greater tolerability, against a backdrop of similar efficacy, is particularly promising because compliance and adherence to current antipsychotic treatments are hindered by their often severe side-effect profiles.[4] Nonadherence, in turn, is associated with poorer prognosis (such as a more severe relapsing-remitting course) and worse functional outcomes.[58] A novel antipsychotic without such side-effects could therefore lead to improved adherence and better outcomes. Finally, with a view to understanding the mechanisms by which CBD may have its antipsychotic effects, serum anandamide concentrations were measured before and after treatment in both groups.[53] As predicted by the authors, anandamide levels were significantly higher in the CBD-treated group relative to the amisulpride group, but perhaps more interesting was the finding of a significant association between the increase in anandamide and reduction in psychotic symptoms in the CBD group ($p = 0.0012$).[53] These findings support the idea that the antipsychotic effects of CBD may be related to its inhibition of anandamide degradation.[53] This concurs with previous work showing that anandamide levels are increased in psychotic disorders (as reviewed by Minichino and colleagues)[8] with higher levels associated with less severe symptomatology.[59–62]

CBD as adjunctive treatment. More recently, in a 6-week multicentre, randomised, double-blind, parallel-group trial, CBD (1000 mg/day; $n = 43$) was compared with placebo ($n = 45$) as an add-on treatment to existing antipsychotic regimens in patients with schizophrenia.[55] There was a significant reduction in PANSS positive symptoms from baseline to 6-week study endpoint in the CBD compared with the placebo group (PANSS treatment difference $= -1.4$, 95% CI $= -2.5$ to -0.2; $p = 0.019$). CBD-treated patients were also more likely to have been rated as improved (Clinical Global Impression Scale; CGI-I treatment difference $= -0.5$, 95% CI $= -0.8$ to -0.1; $p = 0.018$) and as not severely unwell (-0.3, 95% CI $= -0.5$ to 0.0; $p = 0.044$) by the treating clinician.[55] Although the magnitude of these effects appears modest, it is common for treatments to fail in add-on trial designs because the tested treatment needs to show an effect over and above that of the existing treatment (here, antipsychotics, which have relatively large effect sizes).[4,63,64] The fact that CBD produced such an additional effect over that of concomitant antipsychotic treatment is therefore promising. There were also numerical (but nonsignificant) increases in the level of general functioning [Global Assessment of Functioning (GAF) scale treatment difference $= 3.0$, 95% CI $= -0.4$ to 6.4; $p = 0.08$] and cognitive performance in the CBD treatment arm compared with the placebo arm, but no significant differences emerged in a number of other outcomes, including on negative,

Table 1. Overview of studies investigating cannabidiol in patients with psychosis.

Study	Design	CBD regimen	Outcome assessment	Results
Zuardi[48]	One patient with schizophrenia; open label case-report	Up to 1500 mg/day for 4 weeks	BPRS	Significant reduction in positive symptoms
Zuardi[49]	3 treatment-resistant patients with schizophrenia; open-label monotherapy case series	Up to 1280 mg/day for 4 weeks	BPRS	Mild improvement in one patient, no response in two patients
Zuardi[50]	Six patients with Parkinson's disease with psychotic symptoms; open-label pilot study	Up to 600 mg/day for 4 weeks	BPRS, Parkinson Psychosis Questionnaire	Significant reduction in psychotic symptoms
Zuardi[51]	Two patients with bipolar I disorder experiencing a manic episode with psychotic features; rater-blinded case series	Up to 1200 mg/day for 24 days	Young Mania Rating Scale, BPRS	No symptomatic improvement after CBD monotherapy either alone ($n = 1$) or in addition to improvements following CBD plus olanzapine ($n = 1$)
Hallak[52]	28 patients with schizophrenia; baseline performance compared with that after placebo ($n = 10$), 300 mg CBD ($n = 9$) or 600 mg CBD ($n = 9$) administration 1 month later	Single dose of 300 or 600 mg	Stroop Colour Word Test	Stroop test performance significantly improved in placebo and 300 mg CBD group; numerical (nonsignificant) improvement in 600 mg CBD group
Leweke[53]	39 patients with schizophrenia; randomised, double-blind, monotherapy trial of CBD ($n = 19$) compared with the antipsychotic amisulpride ($n = 20$)	Up to 800 mg/day for 4 weeks	BPRS, PANSS	Significant reduction in positive, negative, total and general symptoms in both groups. Significantly fewer side-effects in CBD group
Leweke[54]	29 patients with schizophrenia; randomised, double-blind, placebo-controlled crossover study	600 mg/day for 2 weeks	PANSS	Numerical but nonsignificant improvement in psychotic symptoms associated with CBD treatment
McGuire[55]	88 patients with schizophrenia; randomised, double-blind trial of add-on CBD ($n = 43$) *versus* placebo ($n = 45$)	1000 mg/day for 6 weeks	PANSS, CGI, GAF, Cognition	Significant reduction in positive symptoms and CBD-treated patients more likely rated as improved/not as severely unwell by treating clinicians (CGI)
Boggs[56]	36 patients with schizophrenia; randomised, double-blind trial of add-on CBD ($n = 18$) *versus* placebo ($n = 18$)	600 mg/day for 6 weeks	PANSS, MATRICS	No effects of CBD on cognition or positive, negative or total symptoms
Bhattacharyya[57]	33 patients at CHR for psychosis; randomised, double-blind design; 16 CHR subjects assigned to CBD and 17 to placebo; 19 controls	Single dose of 600 mg	fMRI (brain activation during verbal learning task)	CBD normalised brain function in CHR individuals in regions where CHR individuals showed abnormal activation under placebo

BPRS, Brief Psychiatric Rating Scale; CBD, cannabidiol; CGI, Clinical Global Impression Scale; CHR, clinical high risk; fMRI, functional Magnetic Resonance Imaging; GAF, Global Assessment of Functioning Scale; MATRICS, MATRICS Consensus Cognitive Battery (MCCB); PANSS, Positive and Negative Syndrome Scale.

total and general PANSS scores.[55] The number of adverse events was similar between the CBD (30 adverse events in 15 patients) and the placebo (35 adverse events in 16 patients) treatment arms, with the most common side effects including diarrhoea, nausea and headache. Most side effects were mild and did not require intervention.

Using similar methodology in a 6-week, randomised, parallel-group trial, Boggs and colleagues compared 600 mg/day adjunctive CBD *versus* placebo in 36 stable, antipsychotic-treated patients with chronic schizophrenia.[56] In this latter study, there were no effects of adjunctive CBD relative to placebo on positive, negative or total PANSS symptoms, nor were there any effects on cognitive performance (the primary outcome of the trial, measured using the MATRICS consensus battery; MCCB). In fact, only the placebo group were found to have improved MCCB composite scores over time, which the authors suggest may be due to regression to the mean or practice effects, with this pattern not seen in the CBD group, perhaps due to increased sedation or inhibited learning effects.[56] Overall, CBD was well tolerated, with no worsening of psychosis, mood, suicidality or movement side effects.

The reasons for the contrasting results with the two larger clinical trials remain unclear and warrant consideration.[53,55] One factor could be the lower CBD dose (600 mg/day) used by Boggs and colleagues,[56] compared with the higher doses of 800 and 1000 mg/day in the earlier trials.[53,55] While 600 mg (even as a single acute dose) has been shown to modulate brain function across a variety of tasks in healthy individuals, and can prevent the acute induction of psychotic symptoms following THC,[24] it is possible that a higher therapeutic dose is needed in the context of patients with psychosis.[56] This is consistent with the results from a further earlier study, which also used 600 mg/day in patients with schizophrenia, and which showed nonsignificant results for total PANSS symptom reduction,[54] although there were also a number of design issues associated with this study. Research conducted outside of the psychosis literature suggests that specific effects of CBD follow an inverted-U dose-response curve. This could have pragmatic implications for CBD as a novel pharmacotherapy because individual-patient dose titration would introduce practical challenges in the clinic. In two studies testing multiple doses of acute CBD against anxiety induced by public speaking, only the intermediate doses of CBD (300 mg) significantly reduced anxiety while lower and higher doses did not.[65,66] Animal models of anxiety confirm this dose-response effect, with anxiolytic effects observed at lower doses which disappear at higher doses.[12,67] However, the dose-response range is thought to be narrower for the anxiolytic compared with the antipsychotic effects of CBD,[67,68] at least in preclinical studies.[28] Higher doses are also likely required for antipsychotic *versus* anxiolytic effects (for review see Crippa and colleagues).[12] Future research is required to determine the precise dose-response ranges for specific therapeutic (i.e. antipsychotic and anxiolytic) effects for specific psychotic disorders and other clinical popluations.[12]

Other possible factors that may explain lack of beneficial effect of CBD treatment in the study by Boggs and colleagues may relate to illness stage and symptom severity of the respective samples.[56] The participants in the negative Boggs and colleagues study were older (mean age = 47) and had chronic schizophrenia with stable symptoms, whereas those in the study of Leweke and colleagues were younger (mean age = 30) and were included only if they specifically had an acute exacerbation of psychotic symptoms.[53] This is reflected in the higher mean baseline symptom scores in the Leweke study (PANSS total = 93; positive = 24) compared with the Boggs and colleagues study (total = 80; positive = 20).[53,56] However, the negative findings are harder to reconcile with the positive findings of McGuire and colleagues,[55] where the levels of symptoms were comparable (PANSS total = 80; positive = 18) and the mean age was 41 years. The Boggs and colleagues and McGuire and colleagues studies also took a similar methodological approach (add-on design),[55,56] although the McGuire study had much higher statistical power ($n = 88$ *versus* $n = 36$). Together, these findings may suggest that younger patients in an earlier stage of illness may benefit more from CBD treatment, potentially because intervening early arrests pathophysiological processes before more severe or enduring neural changes (that may be less amenable to later intervention) take place.[5] A further potential difference between the studies relates to the existing antipsychotic treatment regimens within the add-on design. While McGuire and colleagues provide specific data on the exact antipsychotic medications used by their sample, only summary classification data are provided by Boggs and colleagues.[55,56] Nevertheless, in comparison, over 90% of the antipsychotics used in both the

CBD and placebo groups from the McGuire study were second-generation, and only ~8% were first-generation. However, in the Boggs study, 55% of the CBD group and 72% of the placebo group were taking second-generation antipsychotics, while 50% of the CBD group and 28% of the placebo group were taking first-generation. Current evidence suggests there are small but significant differences in efficacy between different individual antipsychotics within both first and second-generation classifications.[4] It is therefore possible that the different baseline mix of concurrent antipsychotics could be a contributing factor to the disparity in results.

Potential effects of CBD on cognition

The psychopathology associated with psychotic disorders is often thought of in terms of positive and negative symptoms. However, cognitive dysfunction is a prominent feature that is strongly associated with loss of social/occupational function and disability.[69,70] Cognitive symptoms are also refractory to any type of current treatment.[2] A number of initial studies have examined whether CBD may improve aspects of cognition in patients with psychosis.

As outlined above, the clinical trial by Boggs and colleagues observed no significant effects of CBD on cognition, which was the study's primary outcome.[56] The largest clinical trial of CBD in patients with psychosis also assessed cognition, using the Brief Assessment of Cognition in Schizophrenia (BACS).[55] While there were no statistically significant effects of CBD on cognition overall, there were numerical increases in BACS composite score, motor speed performance and executive functioning in the CBD relative to the placebo group.[55] Studies of CBD administration in healthy people also show that CBD can attenuate the acute amnestic effects of THC administration,[23] while it does not appear to affect learning and memory in the absence of existing impairments.[71]

A separate study examined the acute effects of a single dose of CBD on cognitive function in 28 patients with schizophrenia.[52] Performance on the Stroop Colour Word Test, which indexes selective attention, was compared at baseline (no drug) to one of three parallel-arm conditions 1 month later: placebo ($n = 10$), 300 mg CBD ($n = 9$) and 600 mg CBD ($n = 9$). While performance improved (numerically) in all three arms from baseline to the second session, indicating a learning effect, only those receiving placebo and the lower CBD dose (300 mg) showed a statistically significant improvement.[52] The authors suggest that sedative effects of CBD may underlie the lack of improvement (related to learning/practice effects) in the higher-dose CBD group. Overall, whether CBD has beneficial effects on cognition in patients with psychosis is currently unclear and remains an important avenue for future research.

Early intervention: prior to psychosis onset

CBD has also been indicated for use prior to the onset of psychosis in patients at clinical high risk for the disorder. These individuals present with clinically significant attenuated psychotic symptoms and have 20–30% risk of developing psychosis within 2 years.[72] Accumulating evidence suggests that the pathophysiological processes driving psychosis evolve over the course of the disorder, with the clinical high-risk state offering a unique opportunity for preventative intervention.[5] However, recent meta-analyses have concluded that existing treatments are not effective for preventing transition to psychosis nor for reducing symptoms,[73,74] representing a significant unmet clinical need. Furthermore, because many of these individuals will not transition to psychosis, pharmacotherapies also need to be safe and well tolerated.

Using a randomised, double-blind, placebo-controlled, parallel-arm design, 33 antipsychotic-naive individuals at clinical high risk for psychosis and 19 healthy controls were studied using a verbal learning fMRI task.[57] A total of 16 high-risk subjects received a single oral dose of CBD (600 mg) and 17 received placebo. Control participants were not given any drug. The results showed that a single dose of CBD normalised brain function in clinical high-risk individuals in regions where high-risk individuals showed abnormal activation under placebo conditions. These specific regions, including the hippocampus, midbrain and striatum, are also strongly implicated in the pathophysiology of psychosis onset.[75,76] The normalisation of aberrant brain function in these regions by CBD could underlie the therapeutic effects observed in previous studies in patients with established psychosis and anxiety disorders.[53,55,77]

In terms of effects following continued treatment, results from the same study investigating the effect of 3-week treatment with CBD (600 mg/day) on symptoms and functional brain activation are

awaited.[78] In summary, initial evidence supports CBD as a potential novel treatment for people at clinical high risk for psychosis, and its benign side-effect profile as evident from other data (see below) makes it a particularly suitable candidate treatment for this patient group. Whether CBD can actually alter the course of the disorder and prevent the onset of psychosis will require larger-scale clinical trials over longer durations. Such studies have recently been initiated and the results are anticipated to make a significant contribution to the evidence base.

Psychosis in nonschizophrenia spectrum disorders

Additional complementary evidence for the use of CBD in psychosis comes from a study of Parkinson's disease psychosis. In a small, open-label pilot study, six patients with Parkinson's disease psychosis received oral CBD for 4 weeks, titrated from a mean dose of 150–400 mg/day in addition to their current treatment regimens.[50] CBD was associated with a significant decrease in psychotic symptoms and was well tolerated, with no side effects clinically observed. CBD also improved total scores on the Unified Parkinson's Disease Rating Scale and did not worsen cognition or motor function. While caution is warranted due to the small sample size and lack of placebo control, these results support the view that CBD is safe, well-tolerated and may have efficacy for the treatment of psychosis in non-schizophrenia spectrum disorders. Phase II clinical trials of CBD for Parkinson's disease psychosis and behavioural symptoms (including psychotic symptoms) in Alzheimer's disease are now being planned.

In addition to its antipsychotic properties, the wider pharmacological profile of CBD, which includes anxiolytic, sedative, anticonvulsant and thus potential mood-stabilising effects, raises the possibility of therapeutic potential for bipolar disorder (with or without psychosis) as well as unipolar mood disorders.[12,79] Aside from anecdotal reports,[79] CBD has so far been tested in two patients with bipolar I disorder experiencing a manic episode with psychotic features.[51] Two female inpatients received placebo for 5 days, followed by oral CBD titrated from 600 to 1200 mg/day for 24 days. One patient received concomitant olanzapine between day 6 and 20, while the other patient did not. Symptoms were assessed using the BPRS and Young Mania Rating Scale. CBD provided no additional benefit over that seen after combined CBD and olanzapine treatment in the first patient, and there was no benefit of CBD monotherapy in the second patient.[51] These negative findings concur with the lack of CBD effects seen in an animal (hyperlocomotion) model of mania.[80] Nevertheless, whether CBD is effective for other specific symptoms in bipolar disorder (such as bipolar depression and anxiety) is currently unknown but clinical trials are now underway.[12] While outside the remit of this review, it is also worth noting that CBD has purported antidepressant-like effects (albeit so far in preclinical studies), thought to be mediated by serotonin 5-HT1A receptors,[81] which could suggest therapeutic potential for mood disorders such as depression.[12,28]

Safety and side effects

While CBD has been found to be safe and well tolerated in the three (relatively short-term) clinical trials in psychosis to date,[53,55,56] the total volume of data is still small and thus insufficient adverse events may yet have accumulated. When measured in terms of 'patient-years' (i.e. the number of patients treated with a new drug multiplied by the duration of treatment), data from at least 1000 patient-years or more are recommended for robust estimates of safety and tolerability.[82] This follows the notion that the greater the clinical use and experience of prescribing drugs in different clinical scenarios, the better (and more nuanced) our knowledge of its true risk-benefit profile. However, 1000 patient-years equates to, for example, 1000 patients taking CBD for 1 year or 500 patients for 2 years. The largest RCT of CBD in psychosis to date randomised 43 patients to receive CBD for 6 weeks.[55] This highlights the significant gulf between the current state of knowledge and the benchmark for sufficient risk-benefit evidence. Larger randomised controlled trials with longer durations of treatment are therefore needed.

Considering the wider literature (not restricted to studies in psychosis), doses of up to 1500 mg/day have been well tolerated in humans with few or no side effects, although such doses have mainly been administered to very few patients in case series reports.[28,48,49] The first comprehensive review of CBD-related (*in vivo* and *in vitro*) side effects suggested that CBD is nontoxic in cell lines and has no adverse effects on physiological parameters such as heart rate, blood pressure and

body temperature, gastrointestinal transit, and psychomotor or psychological function.[83] A second review extended these findings and confirmed that overall, CBD has a favourable safety profile.[84] However, CBD is not entirely side-effect free; *in vitro* work suggests that CBD may affect cell viability, fertilisation potential and drug transporter/P-glycoprotein function,[83,84] and reports of (mostly mild) clinical adverse effects are starting to accumulate as the body of available literature becomes substantiated. The most common adverse effects in clinical studies include diarrhoea, tiredness or sedation, and changes in appetite and weight.[83]

Sedation. The idea that CBD may induce sedation is a recurring theme,[52,56] and there are numerous purported links between the endocannabinoid system and the sleep–wake cycle. One of the earliest studies showed that 600 mg of CBD induced sedation in a small sample of healthy people.[85] In people with insomnia, a therapeutic effect suggestive of sedation (increased sleep time, less frequent awakenings) was noted after 160 mg/day CBD.[86] However, other studies have shown that CBD counteracts the sedative effects of THC,[87] and a recent study investigating the effects of 300 mg CBD (*versus* placebo) on the sleep-wake cycle reported no effects on sedation, albeit this was in healthy individuals.[88] A review concluded that this effect is dose-based, with lower doses having a stimulating effect on the sleep–wake cycle, but higher doses having a sedative effect.[89] Given the aforementioned evidence that higher doses of CBD are likely needed to produce antipsychotic effects, particularly in patients with psychotic disorders (e.g. 800 mg/day or more), sedative side effects may be particularly prevalent when used for this indication and warrant further investigation.

Gastrointestinal. Studies in epilepsy report diarrhoea in approximately 15–20% of CBD-treated individuals.[90] In the largest study in patients with psychosis, 9% of those receiving CBD *versus* 4% receiving placebo reported this side effect.[55] While the severity was often mild and resolved without treatment, the one withdrawal (out of $n = 43$) in the CBD group was due to nausea, diarrhoea, abdominal pain and vomiting.[55] Despite the initial review by Bergamaschi and colleagues suggesting no effects on gastric motility,[83] the emerging pattern of findings is that diarrhoea is one of the most common side effects of CBD. This suggests that it does, in fact, increase gastrointestinal transit in humans which could affect its ultimate acceptability.[84]

Hepatic drug metabolism. CBD is a potent inhibitor of CYP3A4 and CYP2D6, which belong to the cytochrome P450 family of enzymes that together metabolise more than 60% of prescribed drugs, including many antidepressants, antipsychotics and benzodiazepines.[91–94] CBD could, therefore, have effects on the circulating concentrations of other medications.[83] In the context of psychosis, where concomitant antipsychotic treatment is likely, such effects could require careful monitoring and dose adjustment.

Liver enzymes. A meta-analysis of studies conducted in epilepsy found that CBD was associated with significantly increased serum aminotransferases, with a risk ratio of 14.14 (95% CI = 4.48–44.60) in studies using 20 mg/kg CBD.[91] While the potential for hepatic toxicity was identified in this meta-analysis, no events within the individual studies met criteria for lasting liver injury (i.e. based on bilirubin).[91] Monitoring of hepatic function, particularly during the first 30 days of treatment, is therefore recommended.[91,95] Given the potentially serious nature and consequences of this potential side effect, future research should attempt to evaluate such effects (and in additional patient populations).

Unregulated over-the-counter CBD products. One consequence of the explosion of public interest in CBD is that a vast array of unregulated products, purporting to contain CBD, are now widely available from online and high-street stores.[96] These products should explicitly not be used for medicinal purposes (for review see Freeman and colleagues)[96] because they are unregulated, not pharmaceutical grade nor produced under good manufacturing practice conditions;[96] their ingredients and dose are uncontrolled, with existing evidence showing that dosage is highly variable and contrary to labelling[97]; and there is the potential for such products to be contaminated with high levels of other cannabinoids (such as THC),[96–98] which could be detrimental to mental health and especially harmful to those with psychotic disorders. At best, such products represent an expensive placebo due to the typically low doses of CBD per administration (e.g. 25 mg/dose compared with 600–1000 mg/day in clinical studies),[48,55,96] but at worst, these products could be actively harmful due to the high risk of contamination with other cannabinoids. This is particularly the case for individuals with psychotic disorders, but also for children, young adults and adolescents, where cannabinoid exposure during

these critical periods of brain development and maturation could have particularly severe and enduring pervasive effects.[99]

In summary, CBD appears to show a favourable safety and tolerability profile but there remains a paucity of data, particularly in terms of chronic exposure in humans. Whether CBD has adverse effects on liver enzymes and hepatic metabolism, and thus potential interactions with other drugs, remains an important avenue for future research. Going forward, future clinical trials should aim to collect explicit information regarding side effects. While these future studies may indeed show that CBD is associated with common gastrointestinal and possibly sedative side effects, the risk–benefit ratio may still be favourable, especially when compared with the current status quo of treatments for psychosis: antipsychotics.

Potential mechanisms underlying the antipsychotic effects of cannabidiol

The idea that CBD may have therapeutic potential emerged from observations that it has opposite effects to THC at the pharmacological/molecular, neural (systems) and behavioural level.[24,28,42] The main molecular target for THC is the CB1 receptor, where it has partial agonist effects.[25] The molecular mechanisms of CBD are less clear, but its demonstrable ability to attenuate the effects of THC led to the notion that it may be an inverse agonist/antagonist at CB1 receptors. Although, in contrast to THC, CBD has low affinity for CB1,[25] it does appear to 'antagonise the agonists' of this receptor even at relatively low concentrations,[100] potentially *via* negative allosteric modulation.[101]

Another mechanism by which CBD may have antipsychotic effects is *via* upregulation of the endocannabinoid anandamide, likely by inhibiting its degrading enzyme, fatty acid amide hydrolase.[53,102] This is consistent with the aforementioned findings of Leweke and colleageus,[53] where CBD increased serum anandamide levels in patients with psychosis, with this increase significantly associated with the concomitant reduction in psychotic symptoms. Additional pharmacological effects of CBD that have been described include activation of 5-HT1A receptors,[103] transient receptor potential vanilloid type 1,[102] GPR55 receptors and potentially various other mechanisms.[25,104,105,106]

CB1 receptors are widely expressed in brain with the highest concentrations in mesocorticolimbic regions.[107–110] Consistent with this distribution, based on human experimental studies involving cannabinoid administration, CB1 receptors appear to be involved in numerous cognitive processes subserved by corticolimbic circuitry,[44,111] such as learning and memory,[24,47] salience processing,[39,40] and response inhibition,[24] which are also known to be impaired in patients with psychosis.[111] Abundant evidence from experimental studies of healthy volunteers shows that CBD modulates brain function (in the opposite direction to THC) during each of these cognitive processes in their respective neural substrates.[24,39,40,47] This suggests that, at the brain systems level, the mechanism of the antipsychotic effects of CBD may be mediated through modulation of function of these neural substrates. Consistent with this, in patients at clinical high risk for psychosis, CBD was also found to normalise activation in key brain regions strongly implicated in psychosis onset and psychotic symptoms (such as the hippocampus, midbrain and striatum).[57,75,76]

Conclusion

Initial clinical trials suggest that CBD is safe, well-tolerated and may have antipsychotic effects in patients with psychosis. There is some indication that CBD may be particularly effective in the early stages of the disorder, such as in patients at clinical high risk and those with first episode psychosis. Neuroimaging research suggests that CBD may exert its therapeutic effects *via* modulation of brain function in regions known to be altered in patients with psychosis across a variety of cognitive paradigms. Questions remain regarding the full side-effect profile of CBD, with reports of increased liver enzymes and potential for hepatic toxicity, but the most commonly reported side effects (such as diarrhoea and sedation) are likely to be both mild and benign. A more substantial body of evidence, including larger studies with longer-term CBD administration (e.g. up to 2 years), is required to accurately estimate the risk-benefit profile of CBD. Pending such evidence, if CBD treatment were ultimately associated mainly with common sedative and gastrointestinal side effects, these would likely still indicate a favourable tolerability profile compared with the side-effect profiles of currently licensed antipsychotic treatments. Given that CBD has antipsychotic effects without directly acting on dopamine receptors, it could represent

a completely novel class of treatment for psychosis. CBD may also have therapeutic value prior to the onset of frank psychosis in patients at clinical high risk for the disorder, and in patients with nonschizophrenia spectrum disorder psychosis, such as Parkinson's disease. Unregulated over-the-counter products containing CBD should explicitly not be used for medicinal purposes. In sum, CBD currently represents a promising potential novel treatment for patients with psychosis. If the success observed in initial clinical studies are replicated in large-scale trials with chronic administration, CBD has the potential to become the first licensed nondopaminergic treatment for psychosis.

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The authors declare that there is no conflict of interest.

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