Review

A systematic review of the antipsychotic properties of cannabidiol in humans

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ABSTRACT

Despite extensive study over the past decades, available treatments for schizophrenia are only modestly effective and cause serious metabolic and neurological side effects. Therefore, there is an urgent need for novel therapeutic targets for the treatment of schizophrenia. A highly promising new pharmacological target in the context of schizophrenia is the endocannabinoid system. Modulation of this system by the main psychoactive component in cannabis, Δ9-tetrahydrocannabinol (THC), induces acute psychotic effects and cognitive impairment. However, the non-psychotropic, plant-derived cannabinoid agent cannabidiol (CBD) may have antipsychotic properties, and thus may be a promising new agent in the treatment of schizophrenia. Here we review studies that investigated the antipsychotic properties of CBD in human subjects. Results show the ability of CBD to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration. In addition, CBD may lower the risk for developing psychosis that is related to cannabis use. These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex. The first small-scale clinical studies with CBD treatment of patients with psychotic symptoms further confirm the potential of CBD as an effective, safe and well-tolerated antipsychotic compound, although large randomised clinical trials will be needed before this novel therapy can be introduced into clinical practice.

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1. Introduction

Schizophrenia is a chronic mental disorder that typically presents in early adulthood or late adolescence. Although the incidence of schizophrenia is relatively low (10–22 per 100 000), its prevalence is relatively high (0.3–0.7 per 100) due to the chronic nature of the illness (McGrath et al., 2008). It is characterized by a wide range of symptoms, including disturbances of thought, perception, volition, and cognition (see for reviews Tandon et al., 2009; van Os and Kapur, 2009). Because of the pervasiveness of associated impairments and frequently life-long course, it is among the top ten leading causes of disease-related disability in the world. Although extensive research has been performed, its aetiology and pathophysiology remain relatively unclear, and available treatments are only modestly effective and cause serious metabolic and neurological adverse effects (Tandon et al., 2008).

A promising new pharmacological target in the context of schizophrenia is the endocannabinoid system. This neurotransmitter system consists of at least two types of receptors (CB1 and CB2) and endogenous ligands that bind to these receptors (Kano et al., 2009; Katona and Freund, 2012). Whereas CB2 receptors are more pronounced in peripheral regions, CB1 receptors are found throughout the central nervous system, with the highest concentrations demonstrated in the basal ganglia, cerebellum, hippocampus and cortex (Herkenham et al., 1991; Glass et al., 1997; Wong et al., 2010). The two most important endogenous cannabinoid ligands are anandamide and 2-arachidonoyl glycerol (2-AG). They act as retrograde messengers, which means that they are synthesised and released postsynaptically and bind to presynaptic receptors, thereby regulating the release of both inhibitory and excitatory neurotransmitters (Kano et al., 2009; Katona and Freund, 2012). The endocannabinoid system is thought to be involved in many brain functions such as mood, memory and reward processing (Hill et al., 2009; Zanettini et al., 2011; Bossong et al., 2014a,b).

Evidence is accumulating for a role of the endocannabinoid system in the pathophysiology of schizophrenia (Leweke and Koethe, 2008; Bossong and Niesink, 2010). For example, epidemiological studies indicate that the use of cannabis increases the risk for developing schizophrenia (Arseneault et al., 2004; Moore et al., 2007) and lowers the age of onset of the illness (Veen et al., 2004). In patients, cannabis use has been related to higher relapse rates, poor treatment outcome, and increased severity of symptoms (Linszen et al., 1994; D'Souza et al., 2005; Foti et al., 2010), as well as accelerated loss of grey matter

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volume (Rais et al., 2008). In addition, schizophrenia patients show increased levels of endogenous cannabinoids in cerebrospinal fluid (Leweke et al., 1999; Giuffrida et al., 2004). Autoradiography studies with post-mortem brain tissue showed enhanced CB1 receptor densities in schizophrenia patients, with significant increases demonstrated in the dorsolateral prefrontal cortex (Dean et al., 2001; Dalton et al., 2011; Jenko et al., 2012), anterior cingulate cortex (Zavitsanou et al., 2004) and posterior cingulate cortex (Newell et al., 2006). Neuroimaging studies measuring in vivo CB1 receptor availability in schizophrenia patients reported a widespread increase in levels of CB1 receptors, including the nucleus accumbens, insula, cingulate cortex, inferior frontal cortex, parietal cortex, mediotemporal lobe and pons (Wong et al., 2010; Ceccarini et al., 2013).

Although cannabis contains more than 80 different cannabinoid compounds, the principal psychoactive component in cannabis is Δ9-tetrahydrocannabinol (THC), which exerts its effects primarily through action on the CB1 receptor (Ledent, 1999; Huestis et al., 2001). THC is thought to be responsible for the broad range of psychotropic effects of cannabis, such as 'feeling high', relaxation and euphoria, which are considered the main reasons for cannabis use (Green et al., 2003). In addition, THC administration has been shown to induce acute psychotic symptoms (D'Souza et al., 2004; Bhattacharyya et al., 2009; Bossong et al., 2013) and to impair cognitive functions such as learning and memory (Solowij and Michie, 2007; Bossong et al., 2014a). However, recently, another cannabinoid compound has received growing attention: cannabidiol (CBD). Although, unlike THC, CBD is devoid of any psychotropic effects, evidence is increasing that CBD has anxiolytic and antipsychotic properties (Zuardi et al., 2012; Schubart et al., 2014). Although the mode of action of CBD is not fully understood, there are indications that it acts as a cannabinoid CB1/CB2 receptor inverse agonist (Pertwee, 2008), and that it inhibits the uptake and metabolism of anandamide, thereby enhancing levels of endogenous cannabinoids (Bisogno et al., 2001; de Petrocellis et al., 2011; Leweke et al., 2012).

An increasing number of human studies have been performed to provide further insight into the antipsychotic properties of CBD. Although some of these studies have been included in excellent reviews that describe the potential of CBD as a treatment for psychosis in a broader context (Zuardi et al., 2012; Schubart et al., 2014), the aim of the current review is to provide a detailed and up-to-date systematic literature overview of studies that investigated the antipsychotic properties of CBD in human subjects. This included the effect of CBD not only on symptomatology, but also on measures that are known to be affected in schizophrenia patients, such as cognitive function, hippocampal volume or functional brain activity patterns. Papers included in this review are subdivided in the following categories: 1) studies that investigated the impact of CBD/THC ratio in cannabis on measures relevant for psychosis, 2) neuropsychological studies that examined the ability of CBD to block the acute psychotic effects of THC or ketamine in healthy volunteers, 3) neuroimaging studies with acute CBD administration to healthy volunteers, and 4) studies with CBD administration to patients with psychotic symptoms, including small-scale clinical trials with CBD. Finally, methodological issues and recommendations for future research will be discussed.

2. Literature review

2.1. Search strategy

An electronic search was performed using the following criteria in the PubMed database: ("CBD" OR "cannabidiol") AND ("schizophrenia" OR "psychosis"). Reports in English using human subjects published before September 2014 were included. In addition, references of selected papers were examined to ensure the inclusion of other relevant studies.

2.2. Results

A total of 29 studies were identified and included in the current systematic review. Twenty of these studies were found using PubMed and nine studies were added through references in other papers. The latter included for example studies that mentioned 'cannabis potency' rather than 'CBD/THC ratio' and thus did not return from the PubMed search. Please see the Supplementary materials for an overview of included studies.

3. The impact of CBD/THC ratios in cannabis on measures relevant for psychosis

Eight studies have been published that examined the impact of CBD/THC ratios in cannabis on measures relevant for psychosis (Table 1). In a study using hair samples of 140 individuals to analyse levels of cannabinoids, Morgan and Curran (2008) showed that those with only THC in their hair exhibited higher levels of hallucinations and delusions than individuals with both THC and CBD, and those with no cannabinoids (Morgan and Curran, 2008). This finding of lower psychosis-like symptoms in cannabis users with CBD detected in their hair compared with those without was confirmed in another independent study from the same group (Morgan et al., 2012). In a third study from this group, cannabis users (N = 134) were tested 7 days apart on measures of memory and psychotic symptoms, once while they were drug free and once while acutely intoxicated by their own chosen smoked cannabis. Unlike a significant acute memory deficit of individuals who smoked cannabis low in CBD, participants smoking cannabis high in CBD showed no memory impairment. CBD content did not affect psychotic symptoms (Morgan et al., 2010). Schubart et al. (2011) collected data about cannabis use and subclinical psychiatric experiences of 1877 frequent cannabis users in a web-based cross-sectional study. As in the Netherlands concentrations of both CBD and THC are annually measured in different types of cannabis as sold in Dutch 'cannabis cafes' (Pijlman et al., 2005), they were able to estimate CBD and THC exposure of participants. Low CBD content of cannabis was significantly associated with self-reported positive symptoms, but not negative symptoms or depression (Schubart et al., 2011).

In a proton magnetic resonance spectroscopy (^{1}H MRS) study, Hermann et al. (2007) assessed N-acetylaspartate (NAA)/total creatine (tCr) ratios, which is a marker of neuronal integrity, as well as performance on neuropsychological tests and CBD and THC concentrations in hair of 13 cannabis users and 13 controls. In addition to a significantly diminished NAA/tCR ratio in the dorsolateral prefrontal cortex of cannabis users, which is consistent with ^{1}H MRS findings in schizophrenia patients, NAA/tCr ratios in putamen/globus pallidus were positively correlated with CBD hair levels. Furthermore, higher CBD concentration was associated with improved performance on the D2 test for attention and concentration, but impaired performance on the Wisconsin Card Sorting Task (Hermann et al., 2007). Using voxel based morphometry (VBM) in 11 recreational cannabis users and 13 controls, Demirakca et al. (2011) demonstrated a significant correlation between lower CBD/THC ratios as measured in hair and lower right hippocampal volume as well as bilateral hippocampal grey matter concentrations, which have consistently been shown in schizophrenia patients (Demirakca et al., 2011).

In a case–control study with 280 people with a first episode of psychosis and 174 controls, Di Forti et al. (2009) showed that patients were significantly more likely to have used high-potency cannabis, containing high THC and low CBD concentrations, compared to controls who preferred resin (hash), usually containing equal amounts of THC and CBD. In addition, psychosis was associated with more frequent and longer use of cannabis (Di Forti et al., 2009). A second study from this group with 410 first episode psychosis patients revealed that the

Table 1
Studies examining the impact of CBD/THC ratios in cannabis on measures relevant for psychosis.

Study	Assessment	N	Main findings
Hermann et al. (2007)	Hair sample analysis, NAA/tCr ratio measured with ^{1}H MRS, neuropsychological tests	13 users, 13 HCs	↑ CBD = ↑ NAA/tCr ratio in putamen/globus pallidus, ↑ D2 test for attention and concentration, ↓ Wisconsin Card Sorting Task
Morgan and Curran (2008)	Hair sample analysis, Oxford Liverpool Inventory of Life Experiences (OLIFE), Peter's Delusion Inventory (PDI)	140 users	THC only = ↑ hallucinations and delusions, compared to both combination of CBD and THC and no cannabinoids.
Di Forti et al. (2009)	Cannabis Experience Questionnaire	280 FEP, 174 HCs	FEP used higher potency cannabis, for a longer period and more frequent.
Morgan et al. (2010)	Prose recall, source memory, Psychotomimetic States Inventory (PSI) after smoking of their own cannabis	134 users	↑ CBD = absence of memory impairment. No effects on psychotic symptoms.
Demirakca et al. (2011)	Hair sample analysis, hippocampal volume and grey matter concentrations measured with VBM	11 users, 13 HCs	↓ CBD/THC ratio = ↓ right hippocampal volume, ↓ bilateral hippocampal grey matter concentrations
Schubart et al. (2011)	Community Assessment of Psychic Experiences (CAPE)	1877 users	↓ CBD = ↑ self-reported positive symptoms, but not negative symptoms or depression
Morgan et al. (2012)	Hair sample analysis, prose recall, source memory, Schizotypal Personality Questionnaire (SPQ), Brief Psychiatric Rating Scale (BPRS)	120 users	↑ CBD = ↓ psychosis-like symptoms (in recreational users with high THC only)
Di Forti et al. (2014)	Cannabis Experience Questionnaire	410 FEP	↓ CBD/THC ratio = ↓ age of onset of psychosis

CBD, cannabidiol; FEP, first episode psychosis patients; HC, healthy control; ^{1}H MRS, proton magnetic resonance spectroscopy; NAA, N-acetylaspartate; tCr, total creatine; THC, Δ9-tetra-hydrocannabinol; VBM, voxel based morphometry.

use of high potency cannabis, containing less CBD, also resulted in an earlier age of onset of psychosis (Di Forti et al., 2014).

Altogether, studies that examined the impact of CBD/THC ratios in cannabis on measures relevant for psychosis indicate that the use of cannabis with high CBD content is associated with significantly fewer positive symptoms such as delusions and hallucinations, better cognitive function and both lower risk for developing psychosis as well as a later age of onset of the illness compared to cannabis with low CBD/THC ratios. Neuroimaging studies suggest a correlation between higher CBD content and both better neuronal integrity in the striatum as indicated by NAA/tCR ratios and lower hippocampal volume and grey matter density. However, whereas the association between CBD content and the experience of psychosis-like symptoms later in life has repeatedly and independently been demonstrated (Morgan and Curran, 2008; Schubart et al., 2011; Morgan et al., 2012), other findings need confirmation in new cohorts. Finally, the only study that examined the impact of CBD/THC ratios in cannabis on acute behavioural and cognitive effects used a naturalistic approach, and remarkably did not find significant differences on psychotomimetic effects between groups smoking cannabis with low and high CBD (Morgan et al., 2010). Therefore, randomised, placebo-controlled, cross-over pharmacological studies with administration of different types of cannabis are needed in order to further elucidate the role of CBD/THC ratios in the experience of acute psychosis-like symptoms.

4. Neuropsychological studies with acute CBD administration to healthy volunteers

Seven neuropsychological studies have been published that investigated the ability of CBD to block the acute psychotic effects of either THC or ketamine in healthy volunteers (Table 2). In the seventies, Karniol et al. (1974) were the first to investigate this. Forty healthy volunteers were orally administered either placebo, THC (30 mg), CBD (15, 30 or 60 mg) or a combination of THC and CBD. THC administration induced strong psychological reactions and significantly impaired performance on a time production task in which subjects were instructed to estimate 60-second time intervals. Both effects were blocked when THC was given in combination with CBD (Karniol et al., 1974). Dalton et al. (1976) examined the potential of CBD in a series of two experiments. In the first study, simultaneous inhalation of CBD (150 μg/kg) and THC (25 μg/kg) attenuated the subjective euphoria of THC and showed a trend towards a decrease in THC-induced psychomotor impairment (N = 15). When in a second experiment CBD was given 30 min before THC using the same doses and administration method, no effects of CBD were observed (N = 8) (Dalton et al., 1976). Zuardi et al. (1982)

measured subjective and physiological effects after oral administration of placebo, THC (0.5 mg/kg), CBD (1 mg/kg) or a combination of THC and CBD in eight healthy volunteers. CBD was able to block self-reported behavioural changes including anxiety and psychosis-like effects, but not effects on heart rate induced by THC (Zuardi et al., 1982). Leweke et al. (2000) showed that 200 mg of oral CBD was able to decrease the impairment in binocular depth inversion, which is a model of impaired perception during psychotic states, induced by 1 mg of oral nabilone, a synthetic form of THC (N = 9) (Leweke et al., 2000). Roser et al. (2009) demonstrated reduced psychomotor performance as measured with a finger tapping test, which is a consistent finding in schizophrenia patients (Goode et al., 1981), after oral administration of cannabis extract (10 mg THC and 5.4 mg CBD) but not after 10 mg of THC only (N = 24) (Roser et al., 2009). In a small study with six healthy volunteers, Bhattacharyya et al. (2010) reported that pre-treatment with CBD (5 mg, administered 5 min before THC) prevented the induction of psychotic symptoms 30 min after the administration of THC (2.5 mg, both administered intravenously) as measured with the Positive And Negative Syndrome Scale (PANSS) (Bhattacharyya et al., 2010). Hallak et al. (2011) examined the impact of oral CBD pre-treatment (600 mg, administered 65 min before ketamine) on acute behavioural effects of intravenous ketamine administration, which is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that produces symptoms similar to those observed in schizophrenia. CBD increased psychomotor activation produced by ketamine, but showed a non-significant trend to reduce ketamine-induced depersonalisation (Hallak et al., 2011). Using a between-subjects design, Englund et al. (2012) showed that both paranoia and impairment of episodic memory induced by intravenous THC administration (1.5 mg) were inhibited with oral CBD pre-treatment (600 mg, administered 3.5 h before THC) compared to placebo. In addition, clinically significant positive symptoms (≥3 points increase in PANSS positive scores) were less common in the CBD group (Englund et al., 2012).

Altogether, neuropsychological studies with CBD administration in healthy volunteers indicate that CBD has the ability to attenuate acute psychotic and anxiogenic effects as well as cognitive impairment induced by the administration of THC. However, some methodological aspects need to be taken into account when interpreting the findings of the studies discussed in this paragraph. First, the time interval between the administration of compounds seems to play a significant role in the effects of CBD, with a stronger impact of CBD when CBD and THC are given simultaneously (e.g. Karniol et al, 1974; Zuardi et al., 1982; Leweke et al., 2000). This is particularly suggested by the study of Dalton et al. (1976), where CBD attenuated THC-induced

Table 2
Neuropsychological studies with acute CBD administration to healthy volunteers.

Study	Assessment	Administration	Drug interval	N	Main findings
Karniol et al. (1974)	Pulse rate, psychological reactions, time production task	Oral CBD 15, 30 or 60 mg THC 30 mg	0	40[a]	THC-induced psychological reactions and impaired task performance ↓ by CBD
Dalton et al. (1976)	Subjective euphoria, psychomotor function	Inhalation CBD 150 μg/kg THC 25 μg/kg	0 30 min[b]	15 8	THC-induced euphoria ↓ by CBD THC-induced effects not altered by CBD
Zuardi et al. (1982)	Physiological and subjective effects	Oral CBD 1 mg/kg THC 0.5 mg/kg	0	8	THC-induced subjective effects ↓ by CBD
Leweke et al. (2000)	Binocular depth inversion	Oral CBD 200 mg THC 1 mg	0	9	THC-induced impairment in binocular depth inversion ↓ by CBD
Roser et al. (2009)	Psychomotor performance measured with finger tapping task	Oral CBD 5.4 mg/THC 10 mg THC 10 mg	N/A[c]	24	Right-hand tapping frequencies ↓ after cannabis extract but not after THC
Bhattacharyya et al. (2010)	Positive And Negative Syndrome Scale (PANSS)	Intravenously CBD 5 mg THC 1.25 mg	5 min	6	THC-induced psychotic symptoms ↓ by CBD
Hallak et al. (2011)	BPRS, CADSS	CBD 600 mg oral Ketamine intravenously[d]	65 min	10	Ketamine-induced psychomotor activation ↑ by CBD
Englund et al. (2012)	Positive And Negative Syndrome Scale (PANSS)	CBD 600 mg oral THC 1.25 mg intravenously	3.5 h	48[e]	THC-induced paranoia, memory impairment and clinically significant positive symptoms ↓ by CBD

BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative States Scale; CBD, cannabidiol; THC, Δ9-tetrahydrocannabinol.
[a] Assigned to one of eight experimental groups, resulting in 5 participants per group.
[b] Two different experiments were reported in one paper.
[c] Assessed in two separate sessions.
[d] Bolus of 0.26 mg/kg over 1 min followed by infusion of 0.25 mg/kg over 30 min.
[e] Assigned to one of two experimental groups, resulting in 22 subjects pre-treated with CBD and 26 subjects pre-treated with placebo.

euphoric effects when both drugs were administered simultaneously, but not when CBD was given 30 min before THC (Dalton et al., 1976). These observations are supported by preclinical studies that examined the impact of the time interval between CBD and THC administration on THC effects. For example, pre-treatment with CBD 15 to 60 min before THC administration but not co-administration of both drugs significantly increased brain THC concentrations in both mice and rats. This effect was accompanied by a significant increase in THC-induced immobility when animals were pre-treated with CBD (Reid and Bornheim, 2001). In a more recent study by Klein et al. (2011), adolescent rats were administered increasing doses of THC daily for 21 days, with pre-treatment of either placebo or CBD 20 min prior to each THC injection. Pre-treatment with CBD significantly potentiated inhibition of body weight gain, anxiogenic effects, locomotor suppressant effects and decreased social interaction seen with THC. In addition, CBD pre-treatment augmented blood and brain THC levels and lowered levels of THC metabolites (Klein et al., 2011). In conclusion, both preclinical and clinical findings suggest that CBD may only attenuate acute THC-induced psychotic and anxiogenic effects when administered simultaneously. Second, studies reported in this paragraph used different dose ratios between CBD and THC, ranging from 200 in the study of Leweke et al. (2000) to 0.5 in that of Karniol et al. (1974). Interestingly, this latter study showed that the significant THC-induced enhancement of pulse rate was attenuated when CBD was administered using a CBD/THC dose ratio of 1 to 2 (30 mg THC and either 30 or 60 mg CBD), but was potentiated using a ratio of 0.5 (30 mg THC and 15 mg CBD). In line with this, the only other study using a low CBD/THC ratio showed stronger effects after combined administration of CBD and THC than after THC alone (CBD/THC ratio of 0.5; Roser et al., 2009). A review by Zuardi and Karniol (1984) about the impact of CBD/THC ratios on acute effects of THC further supports this idea of a biphasic response as they conclude that antagonistic effects of CBD are observed with high CBD/THC ratios, whereas low ratios potentiate acute THC effects (Zuardi and Karniol, 1984). Third, different methods of drug administration were applied. Although in most studies CBD and THC were given in

the same manner, two studies used intravenous administration of either THC or ketamine in combination with oral CBD pre-treatment (Hallak et al., 2011; Englund et al., 2012). Whereas Englund et al. (2012) administered THC at the moment of peak CBD plasma concentrations (3.5 h after CBD), Hallak et al. (2011) allowed only 65 min in between drugs, which may have facilitated a potentiation rather than attenuation of ketamine effects. Please note that the administration of CBD alone was associated with minimal psychoactive effects, with increased self-reported ratings on scales measuring how 'quick-witted' and 'clear-minded' participants felt (Zuardi et al., 1982) and decreased self-reported ratings on 'energetic arousal' (Englund et al., 2012) as the only significant effects observed after the administration of CBD only (although the latter was tested vs baseline and not vs placebo).

5. Neuroimaging studies with acute CBD administration to healthy volunteers

Nine studies have been published that investigated the acute effects of CBD on brain function with neuroimaging techniques (Table 3). Three studies were performed with electroencephalography (EEG) and six with functional Magnetic Resonance Imaging (fMRI). Furthermore, one paper was published that described additional analyses of the originally reported fMRI experiments (Bhattacharyya et al., 2010).

An EEG study by Juckel et al. (2007) (N = 22) examined the effects of administration of both THC (10 mg capsule) and cannabis extract (capsule containing 10 mg THC and 5.4 mg CBD) on auditory evoked mismatch negativity (MMN), which reflects auditory information processing, and has been shown to be reduced in schizophrenia patients (Umbricht and Krljes, 2005). Cannabis extract containing both THC and CBD induced significantly greater MMN amplitude at the central but not at the frontal positions compared to placebo. THC only did not significantly alter MMN amplitude. These findings may suggest improved cognitive performance under the influence of cannabis extract, which may thus be driven by CBD, although no significant differences were reported for the direct comparison of THC and

Table 3
Neuroimaging studies with acute CBD administration to healthy volunteers.

Study	Assessment	Administration	N	Main findings
Juckel et al. (2007)	EEG MMN amplitude	Oral CBD 5.4 mg/THC 10 mg THC 10 mg	22	MMN amplitudes ↑ at central EEG electrodes after cannabis extract but not after THC only.
Borgwardt et al. (2008)	fMRI Go/no-go task	Oral CBD 600 mg THC 10 mg	15	CBD vs placebo: superior temporal gyrus L, insula L ↓ Significant drug effects[a]: parahippocampal gyrus LR, insula L, caudate L, with activity ↑ after CBD compared to both placebo and THC
Roser et al. (2008)	EEG P300 during choice reaction task	Oral CBD 5.4 mg/THC 10 mg THC 10 mg	20	No reversal of THC-induced P300 reduction after cannabis extract
Bhattacharyya et al. (2009)	fMRI Paired associate learning task	Oral CBD 600 mg THC 10 mg	15	Significant drug effects during retrieval: striatum LR, lateral prefrontal cortex L, anterior cingulate cortex, with activity ↑ after CBD compared to both placebo and THC in striatum LR
Fusar-Poli et al. (2009)	fMRI Gender discrimination task Skin conductance response	Oral CBD 600 mg THC 10 mg	15	CBD vs placebo: amygdala L, anterior cingulate cortex, posterior cingulate cortex ↓, which correlated with skin conductance response Significant drug effects: amygdala L, fusiform gyrus L, lingual gyrus L, lateral prefrontal cortex L, cerebellum LR
Stadelmann et al. (2011)	EEG P300 during choice reaction task	Oral CBD 5.4 mg/THC 10 mg THC 10 mg	24	P300 amplitude ↓ after THC but not after cannabis extract for those participants displaying long AAT repeats within the CB1 receptor gene (≥10 in both alleles)
Winton-Brown et al. (2011)	fMRI Auditory processing Visual processing	Oral CBD 600 mg THC 10 mg	14	Auditory CBD vs placebo: superior temporal gyrus R, middle temporal gyrus LR, caudate LR, parahippocampal gyrus LR, insula LR ↑; superior temporal gyrus L, middle temporal gyrus L, insula L ↓ Auditory CBD vs THC: middle temporal gyrus R, superior temporal gyrus R, insula R ↑ Visual CBD vs placebo: lingual gyrus R, inferior occipital gyrus, middle occipital gyrus LR, cuneus R, cerebellum R ↑ Visual CBD vs THC: lingual gyrus L, cerebellum L ↑; lingual gyrus LR, cerebellum LR ↓
Bhattacharyya et al. (2012)	fMRI Oddball detection paradigm	Oral CBD 600 mg THC 10 mg	15	CBD vs placebo: medial prefrontal cortex R ↓ Significant drug effects: prefrontal cortex R, with activity ↓ after CBD compared to both placebo and THC; striatum L, (para)hippocampus L, with activity ↑ after CBD compared to both placebo and THC

CBD, cannabidiol; EEG, electroencephalogram; fMRI, functional Magnetic Resonance Imaging; L, left; R, right; THC, Δ9-tetrahydrocannabinol.
[a] Analysed using repeated measures ANOVA including all three conditions (placebo, CBD, THC).

cannabis extract (Juckel et al., 2007). Using the same drugs and administration method in a sample of 20 healthy volunteers, Roser et al. (2008) investigated the effects of CBD on amplitudes of auditory evoked P300 waves during a choice reaction task, which are known to be reduced in schizophrenia patients, indicating deficient resource allocation and active working memory (Polich, 1991). Administration of cannabis extract containing both THC and CBD did not reverse the THC-induced P300 reduction (Roser et al., 2008). In a follow-up study, it was shown that CB1 receptor genotype influenced the sensitivity to the acute effects of cannabinoids on P300 generation, as P300 amplitude was significantly reduced after THC but not after cannabis extract for those participants displaying long AAT repeats (Stadelmann et al., 2011).

In a series of double-blind, pseudo-randomised fMRI experiments, 15 healthy subjects performed several neuropsychological tasks in the scanner after either oral placebo, CBD (600 mg) or THC (10 mg) administration. Using a go/no-go task to study response inhibition, Borgwardt et al. (2008) demonstrated significantly reduced activation after CBD administration in the left temporal cortex and insula compared to placebo (Borgwardt et al., 2008). When analysed using repeated measures ANOVA including all three conditions (placebo, CBD and THC), significant drug effects were shown in the bilateral parahippocampal gyrus, left insula and left caudate. In these areas, THC attenuated activity whereas CBD increased activity relative to placebo (Bhattacharyya et al., 2010). In a verbal paired associate learning task that included encoding and recall conditions, CBD administration did not induce any significant effects on brain activity compared to placebo (Bhattacharyya et al., 2009). However, significant drug effects were demonstrated during the recall condition in the bilateral striatum, left lateral prefrontal cortex, and anterior cingulate cortex. In the striatum, THC reduced activity whereas CBD increased activity relative to placebo (Bhattacharyya et al., 2010). When viewing

intensely fearful faces, CBD significantly attenuated activity in the left amygdala and the anterior and posterior cingulate cortex. The decrease in amygdala and anterior cingulate responses was correlated with a significant reduction in skin conductance response, which is a physiological measure of emotional response (Fusar-Poli et al., 2009). Significant drug effects were demonstrated in the left amygdala, fusiform gyrus, lingual gyrus and lateral prefrontal cortex, and in the bilateral cerebellum. The CBD effect in the amygdala was significantly correlated with a reduction in self-reported feelings of anxiety (Bhattacharyya et al., 2010). Winton-Brown et al. (2011) examined effects of CBD and THC on brain activity patterns during auditory and visual processing. CBD increased activity in the right temporal cortex, including the right-sided homolog to Wernicke's area, during auditory processing and in the right occipital cortex during visual processing, both in comparison to placebo as well as to THC. Activity after CBD was reduced in the left superior temporal gyrus during auditory processing when compared to placebo (Winton-Brown et al., 2011). Bhattacharyya et al. (2012) used a visual oddball detection paradigm to study attentional salience after CBD and THC administration. Relative to placebo, both the reaction time across all presented stimuli and right prefrontal activity were significantly reduced after CBD administration. A direct comparison of CBD and THC conditions revealed increased activity in the left striatal and hippocampal areas and reduced activity in the right prefrontal areas after CBD (Bhattacharyya et al., 2012). Please note that apart from a trend towards a significant reduction in measures of anxiety during the emotional processing task (Fusar-Poli et al., 2009) and lower reaction times during the performance of the salience task (Bhattacharyya et al., 2012), CBD administration did not induce any effects on task performance or ratings of symptomatology.

Altogether, studies that investigated the acute impact of CBD on brain function indicate significant opposite effects of CBD and THC during the performance of tasks that involve cognitive processes

known to be impaired in schizophrenia patients, such as learning and memory, response inhibition and both salience and emotional processing. Contrasting effects of CBD and THC are demonstrated in areas that are thought to be significantly involved in the performance of these tasks, most likely reflecting different engagement of these brain regions under the influence of either compound. For example, activity in the amygdala during emotional processing was increased after THC but reduced after CBD administration, which may reflect their respective anxiogenic and anxiolytic properties, as also discussed in paragraph 4. Along the same lines, CBD and THC displayed opposite effects in striatal, hippocampal and prefrontal areas during salience processing, possibly reflecting enhancement of the appropriate response and aberrant response to salient stimuli, respectively. Interestingly, acute effects of CBD and THC differed significantly in the auditory cortex during processing of auditory information and in the visual cortex during processing of visual information. This may reflect the reported opposite effects of both compounds on psychosis-like symptoms such as hallucinations. Please note that all functional MRI studies discussed in this paragraph examined the acute effects of CBD and THC in separate sessions. Neuroimaging studies that investigate the impact of simultaneous administration of CBD and THC on brain function are warranted.

6. Studies with CBD administration to patients with psychotic symptoms

Five studies have been published in which patients with psychotic symptoms were treated with CBD (Table 4). In a first case report, Zuardi et al. (1995) described symptomatology of a 19-year-old female schizophrenia patient who was treated with CBD for 26 days (maximum of 1500 mg/day orally). CBD treatment resulted in the improvement of symptomatology as measured with the Brief Psychiatric Rating Scale (BPRS). This improvement was not achieved with haloperidol treatment (Zuardi et al., 1995). In a follow-up study from the same group, three treatment-resistant schizophrenia patients were treated with CBD for four weeks (maximum of 1280 mg/day orally). Although all patients tolerated CBD well and no side effects were reported, only one of the three patients showed mild improvement on the BPRS after CBD monotherapy (Zuardi et al., 2006). In a third study, six patients with Parkinson's disease who experienced psychotic symptoms received CBD daily for four weeks (maximum of 600 mg/day orally). CBD treatment significantly decreased symptomatology as measured with the BPRS without any adverse effects (Zuardi et al., 2009). Using a Stroop Colour Word Test, Hallak et al. (2010) tested the effect of single doses of CBD administration on

selective attention in 28 schizophrenia patients. All patients attended two experimental sessions, the first one without the administration of drugs and the second after oral administration of either placebo, 300 mg CBD or 600 mg CBD. Comparison of the first and second sessions revealed improved performance in all three groups, with patients who received placebo and CBD 300 mg performing significantly better than those who received CBD 600 mg. No effects of CBD administration were found on symptomatology (Hallak et al., 2010). In the largest clinical trial with CBD treatment of schizophrenia patients to date, Leweke et al. (2012) performed a double-blind, randomised clinical trial of CBD (N = 20) vs the conventional antipsychotic compound amisulpride (N = 19). After four weeks of treatment (maximum of 800 mg/day orally), both CBD and amisulpride resulted in significant clinical improvement as measured with both the PANSS and BPRS. However, CBD treatment displayed a markedly superior side-effect profile, reflected in significantly smaller changes in extrapyramidal symptoms, weight gain and prolactin levels (Leweke et al., 2012).

Altogether, the first small-scale studies that investigated the potential of CBD as antipsychotic treatment in patients with psychotic symptoms show promising results in that most patients exhibit significant clinical improvement after four weeks of CBD treatment. This in combination with the presence of minimal side effects compared to conventional antipsychotic compounds such as amisulpride seems to make CBD a promising new antipsychotic agent. Large-scale clinical trials with longer CBD treatment are needed to further examine the antipsychotic potential of CBD.

7. Discussion

The current review provides the first systematic literature overview of studies that investigated the antipsychotic properties of CBD in human subjects. Taken together, CBD appears to have the ability to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration. In addition, it may lower the risk for developing psychosis that is related to cannabis use. These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex. The first small-scale clinical studies with CBD treatment of patients with psychotic symptoms further confirm the potential of CBD as an effective antipsychotic compound with minimal side effects.

Neuropsychological studies with acute CBD administration, as discussed in paragraph 4, suggest that simultaneous administration and higher CBD/THC dose ratios are associated with a stronger impact

Table 4
Studies with CBD administration to patients with psychotic symptoms.

Study	Assessment	Oral CBD administration	N[a]	Main findings
Zuardi et al. (1995)	BPRS	Up to 1500 mg/day for 26 days	1	Improvement of symptomatology, no side effects
Zuardi et al. (2006)	BPRS	Up to 1280 mg/day for 4 weeks	3	Mild improvement of symptomatology of 1 patient, no side effects
Zuardi et al. (2009)	BPRS, Parkinson Psychosis Questionnaire (PPQ)	Up to 600 mg/day for 4 weeks	6	Improvement of symptomatology, no side effects
Hallak et al. (2010)	Stroop Colour Word Test, BPRS, PANSS	Single doses of 300 or 600 mg	28[b]	Performance ↑ after placebo and CBD 300 mg compared to CBD 600 mg; no effects on symptomatology
Leweke et al. (2012)	BPRS, PANSS	Up to 800 mg/day for 4 weeks	39[c]	CBD as effective as amisulpride in terms of improvement of symptomatology; CBD displayed superior side-effect profile

BPRS, Brief Psychiatric Rating Scale; CBD, cannabidiol; PANSS, Positive And Negative Syndrome Scale.

[a] All schizophrenia patients apart from Zuardi et al. (2009), which includes patients with Parkinson's disease who experience psychotic symptoms.

[b] All patients attended two experimental sessions, the first one without the administration of drugs and the second after oral administration of either placebo (N = 10), 300 mg CBD (N = 9) or 600 mg CBD (N = 9).

[c] 20 patients assigned to CBD and 19 patients to the conventional antipsychotic compound amisulpride.

of CBD on acute THC effects. Interestingly, studies that examined CBD/THC ratios in cannabis on measures relevant for psychosis, as reviewed in paragraph 3, indicate that the use of cannabis with high CBD content is associated with significantly fewer psychosis-like symptoms as well as a lower risk for developing psychosis. When used as cannabis, CBD and THC are obviously taken simultaneously, but how do CBD/THC ratios used in laboratory studies compare to those in cannabis? In the study of Morgan et al. (2010) where participants smoked their own cannabis, the CBD/THC ratio in the low CBD group was 0.01 (0.1:6.9%) and in the high CBD group 0.55 (4.6:8.4) (Morgan et al., 2010). This is consistent with measures of street cannabis in the Netherlands and the United Kingdom, which show CBD/THC ratios of 0.01 (0.25:21.5%) and 0.05 (0.1:2.1%) in herbal cannabis and 0.44 (8.1:18.5%) and 1.2 (4.2:3.5%) in resin, respectively (Pijlman et al., 2005; Potter et al., 2008). These CBD/THC ratios of cannabis with high CBD are lower than those used in laboratory studies, where CBD/THC ratios between 2 and 6 are more common (Bhattacharyya et al., 2010; Dalton et al., 1976; Zuardi et al., 1982; see Table 2). Given the absence of significant differences on psychotomimetic effects between groups smoking cannabis with low and high CBD (Morgan et al., 2010), one possibility may be that the beneficial effects of CBD at the lower doses at which it occurs in cannabis are cumulative rather than acute effects. Nevertheless, it is highly important to inform cannabis users about the differences in effects and risks between cannabis types, particularly with the use of high-potency cannabis becoming increasingly common worldwide (UNODC, 2013).

As discussed in paragraph 5, in healthy volunteers, opposite effects of CBD and THC have been shown on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex. Not only schizophrenia patients exhibit enhanced CB1 receptor densities in these brain areas, as indicated by both post-mortem autoradiography (Dean et al., 2001; Dalton et al., 2011; Jenko et al., 2012) and in vivo neuroimaging studies (Ceccarini et al., 2013), but also they are more sensitive to the acute effects of THC (D'Souza et al., 2005). This suggests that opposing effects of CBD and THC may even be more evident in patients.

Whereas simultaneous administration of CBD and THC may mitigate the acute effects of THC, longer time intervals between the administration of compounds were associated with the potentiation of THC effects. This suggests that the impact of cannabis may be stronger when CBD is used as antipsychotic medication, which is particularly relevant given the high prevalence of cannabis use among schizophrenia patients (Green et al., 2005). Importantly, in the largest clinical trial with CBD treatment of schizophrenia patients to date, cannabis use was not allowed (Leweke et al., 2012). Future clinical trials with CBD in the context of psychosis that are performed in a more naturalistic setting should therefore include assessments of cannabis experiences.

As already discussed throughout the review, suggestions can be made for future research on the antipsychotic properties of CBD. First, randomised, placebo-controlled, cross-over pharmacological studies with administration of cannabis with different CBD/THC ratios are needed in order to further elucidate the impact of CBD in the experience of acute psychosis-like symptoms. Preferably, these studies also include neuroimaging assessments, as the effects of simultaneous administration of CBD and THC on brain function are currently unknown. Second, large-scale clinical trials with longer CBD treatment are needed to further evaluate the efficacy of CBD as an antipsychotic compound in schizophrenia patients. Alternatively, randomised clinical trials with CBD could be conducted with individuals who are at an ultra-high risk for developing schizophrenia, in order to intervene in a very early phase of the disease and possibly to prevent the risk of later progression to full-blown schizophrenia (McGorry et al., 2009). These trials could encompass neuroimaging measures to examine long-term CBD effects on brain function such as the assessment of striatal dopamine function as measured with Positron Emission Tomography (PET), regional

glutamate concentrations as measured with ^{1}H MRS, or brain activity patterns during performance of cognitive tasks as measured with fMRI. One important aspect to take into account in these clinical trials is whether CBD treatment influences the effects of cannabis.

In conclusion, studies discussed in this review provide support for CBD as an effective, safe and well-tolerated antipsychotic compound. Large randomised clinical trials will be needed before this novel therapy can be introduced into clinical practice.

Contributors

TA managed the literature search and wrote the first draft of the manuscript. MB contributed to the conception of the review and edited the manuscript. Both authors have approved the final manuscript.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.01.033.

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