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Paolo Brambilla, *Section Editor*

Pharmacological properties of cannabidiol in the treatment of psychiatric disorders: a critical overview

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Cannabidiol (CBD) represents a new promising drug due to a wide spectrum of pharmacological actions. In order to relate CBD clinical efficacy to its pharmacological mechanisms of action, we performed a bibliographic search on PUBMED about all clinical studies investigating the use of CBD as a treatment of psychiatric symptoms. Findings to date suggest that (a) CBD may exert antipsychotic effects in schizophrenia mainly through facilitation of endocannabinoid signalling and cannabinoid receptor type 1 antagonism; (b) CBD administration may exhibit acute anxiolytic effects in patients with generalised social anxiety disorder through modification of cerebral blood flow in specific brain sites and serotonin 1A receptor agonism; (c) CBD may reduce withdrawal symptoms and cannabis/tobacco dependence through modulation of endocannabinoid, serotoninergic and glutamatergic systems; (d) the preclinical pro-cognitive effects of CBD still lack significant results in psychiatric disorders. In conclusion, current evidences suggest that CBD has the ability to reduce psychotic, anxiety and withdrawal symptoms by means of several hypothesised pharmacological properties. However, further studies should include larger randomised controlled samples and investigate the impact of CBD on biological measures in order to correlate CBD's clinical effects to potential modifications of neurotransmitters signalling and structural and functional cerebral changes.

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Cannabidiol (CBD) represents the second most abundant phytocannabinoid in *Cannabis* plant after the psychoactive tetrahydrocannabinol (Δ9-THC) and, in recent years, an increasing body of evidences emphasised its promising role as a treatment in several medical conditions (Fasinu *et al.* 2016). Indeed, CBD exhibits various therapeutic effects that range from antioxidant, anti-inflammatory and neuroprotective (Watt & Karl, 2017) to anticonvulsive (Perucca, 2017), anti-emetic (Parker *et al.* 2011) and analgesic (Lötsch *et al.* 2018).

Moreover, several animal studies and clinical trials on healthy controls suggested its potential role as an antipsychotic (Hahn, 2018), anxiolytic (Soares & Campos, 2017) and anti-craving (Lee *et al.* 2017)

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drug, as well as a pro-cognitive (Osborne *et al.* 2017) and antidepressant (de Mello Schier *et al.* 2014) compound. Therefore, it is not surprising that CBD has been considered as a new potential treatment in several psychiatric disorders.

In this regard, in order to link the so far hypothesised pharmacological mechanisms of action of CBD to its clinical effect in psychiatric disorders, we performed a bibliographic search in PubMed using '*Cannabidiol AND Psychiatry*', '*Cannabidiol AND Psychosis*', '*Cannabidiol AND Schizophrenia*', '*Cannabidiol AND Bipolar Disorder*', '*Cannabidiol AND Depression*', '*Cannabidiol AND Anxiety*', '*Cannabidiol AND Substance Use Disorder*', '*Cannabidiol AND Withdrawal Syndrome*' as key words. Additional articles were identified through the reference lists of the papers. We selected published studies from January 1995 until April 2018. We excluded both pre-clinical studies and clinical trials in healthy controls. Fourteen studies were finally included (five case reports, one open-label pilot study, one double-blinded controlled clinical trial, seven randomised double-blinded controlled clinical trials), matching methods and results summarised in Table 1.

CBD and psychosis

Eight studies evaluated the clinical effect of CBD in psychosis. Five of these studies found a beneficial effect of CBD in reducing psychotic symptoms in schizophrenia (SKZ) (Zuardi *et al.* 1995; Leweke *et al.* 2012; Leweke, 2013; McGuire *et al.* 2018) and in Parkinson's disease (Zuardi *et al.* 2009), while the others found only mild effects or no improvement over psychotic symptoms in patients with SKZ (Zuardi *et al.* 2006; Boggs *et al.* 2018) or in bipolar disorder (BD) patients experiencing a manic episode with psychotic features (Zuardi *et al.* 2010).

The majority of studies attributed the potential antipsychotic properties of CBD to its ability to directly inhibit the reuptake of anandamide, an endocannabinoid that exhibits neurogenic and anti-inflammatory activity (Pisanti *et al.* 2017) and plays a major role in mood regulation, cognition and behaviour (Di Marzo & Petrosino, 2007). Moreover, CBD can also reduce endocannabinoids degradation by blocking fatty acid amide hydrolase function (Pisanti *et al.* 2017). Consequently, the increase of endocannabinoids, such as anandamide, in postsynaptic neurons may regulate presynaptic release of γ-aminobutyric acid and glutamate as well as stabilise dopamine neurotransmission (Gururajan & Malone, 2016). Moreover, CBD has low affinity for cannabinoid receptor type 1 (CB1R) and type 2 (CB2R) with a not specific indirect antagonism when these receptors are activated by Δ9-THC (Pisanti *et al.* 2017). Therefore, CBD may likely contrast Δ9-THC psychotropic activity through a non-competitive negative allosteric modulation of CB1R by binding to a distinct allosteric site (Laprairie *et al.* 2015). Furthermore, while the antipsychotic effect of CBD has been mainly related to the enhanced endocannabinoids signalling, some authors recently hypothesised that CBD may exert its antipsychotic action through a partial agonist activity on dopamine D2 receptors, similarly to the atypical antipsychotic aripiprazole (Seeman, 2016), and through the activation of vanilloid receptor 1, a non-selective calcium channel, thus facilitating glutamate pre-synaptic release (Campos *et al.* 2012).

Interestingly, in the study carried out by Leweke *et al.* (Leweke *et al.* 2012), patients with SKZ were randomised to either amisulpride treatment or CBD administration for 28 days. The authors showed that both CBD and amisulpride groups had a significant reduction of psychotic symptoms and no difference in clinical efficacy was detected between the two different treatments. Moreover, the CBD group showed significantly higher serum level of both anandamide and fatty acid amide hydrolase substrates, a result which has been directly related to the CBD antipsychotic properties (Hahn, 2018). Finally, McGuire *et al.* (McGuire *et al.* 2018) detected a significant reduction of positive symptoms in patients with SKZ treated with CBD compared with placebo but the authors did not find any significant correlation between CBD plasma levels or its hydroxyl metabolites (6-OH-CBD, 7-OH-CBD) and the scores of scales assessing psychotic symptoms.

In conclusion, overall these evidences suggest that CBD may exert antipsychotic effects in patients with SKZ (Zuardi *et al.* 1995; Leweke *et al.* 2012; Leweke, 2013; McGuire *et al.* 2018) and Parkinson's psychosis (Zuardi *et al.* 2009). However, in three studies, CBD was ineffective to treat psychotic symptoms in BD patients (Zuardi *et al.* 2010) and outpatients with SKZ (Zuardi *et al.* 2006; Boggs *et al.* 2018). Moreover, the antipsychotic effect of CBD seemed to be related to the endocannabinoids plasma-level increase (Leweke *et al.* 2012), but not to CBD serum levels (McGuire *et al.* 2018). However, these results need further investigations. Therefore, since the facilitation of endocannabinoid signalling was the most likely hypothesised antipsychotic mechanism, the discrepancy of results among studies emphasised the need to evaluate endocannabinoid plasma-level changes in order to detect their potential contribution to the antipsychotic action.

CBD and anxiety disorder

The anxiolytic properties of CBD have been investigated by two clinical studies, carried out by the same

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Table 1. *Summary of the studies described in the manuscript*

Article	Study design	Diagnosis	Sample (M/F)	Age (years old)	CBD dosage/ formulation	CBD timing	Augmentation	Scales, test and measurements	Main results
Zuardi *et al.* (1995)	Case report	Treatment-resistant SKZ	1 (0/1)	19	1500 mg/day of gelatin capsules (with powder CBD dissolved in corn oil)	4 weeks	Diazepam co-medication allowed	BPRS IOSPI UKU	Significant reduction of all items of BPRS score No side effects
Zuardi *et al.* (2006)	Case report	Treatment-resistant SKZ	3 (3/0)	23 23 22	CBD in two daily doses, from 40 mg/ day until 1280 mg/ day	29 days	/	BPRS PANSS-N CGI UKU SAS BARS	Mild or no symptoms improvements No side effects
Zuardi *et al.* (2009)	Open-label pilot study	Parkinson disease with psychotic symptoms	6 (4/2)	58.8 ± 14.9	150 mg/day up to 400 mg/day of gelatin capsules (with powder CBD dissolved in corn oil)	4 weeks	Median of 1050 mg/day of L-dopa	BPRS PPQ UPDRS CGI MMSE FAB	Significant reduction psychotic symptoms. No side effects
Hallak *et al.* (2010)	Double-blinded, placebo-controlled study	SKZ	28 (18/10)	More than 18	300 mg CBD, 600 mg CBD or placebo in gelatin capsules	One single dose	/	BPRS PANSS SCWT	Single acute administration of CBD did not improve SCWT performances. Possible sedative effect with 600 mg dose

Continued

Table 1. *Continued*

Article	Study design	Diagnosis	Sample (M/F)	Age (years old)	CBD dosage/ formulation	CBD timing	Augmentation	Scales, test and measurements	Main results
Leweke *et al.* (2012)	Double-blinded, randomised, parallel-group, controlled clinical trial of CBD *v.* amisulpride	SKZ or schizophreniform psychosis	20 (15/5) CBD group + 19 (17/2) amisulpride group	18–50	200 mg/day up to 800 mg/day CBD or amisulpride	4 weeks	Lorazepam co-medication allowed	BPRS PANSS EPS CGI SAS	Significant clinical improvement in both groups. Anandamide and FAAH substrates levels higher in CBD group. Fewer side effects in the CBD group
Leweke (2013)	Double-blind, randomised, placebo-controlled, cross-over clinical trial pf CBD *v.*	First-episode paranoid SKZ	29	NIA	600 mg/day CBD	14 days	NIA	NIA	CBD improved psychotic symptoms compared with baseline
McGuire *et al.* (2018)	Double-blind, randomised, placebo-controlled, parallel-group trial	SKZ or a related psychotic disorder	43 (28/15) CBD group + 45 (23/22) placebo group	18–65	1000 mg/day CBD (10 mL of a 100 mg/mL oral solution) or placebo in two doses	6 weeks	Antipsychotic medication	PANSS SANS CGI GAF BACS SAS	Significant reduction of positive symptoms, better cognitive performance and overall functioning in CBD group No significant side-effects. No correlations between CBD plasma levels and scale scores
Boggs *et al.* (2018)	Double-blind, randomised, placebo-controlled, parallel group trial	SKZ	18 (12/6) CBD group + 18 (13/5) Placebo group	18–65	600 mg/day oral CBD	6 weeks	Antipsychotic medication	MCCB PANSS	No improvement in cognitive scores and no reduction of psychotic symptoms

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Crippa *et al.* (2011)	Double-blind, randomised, placebo-controlled, repeated measures, within-subjects cross-over trial	Treatment-naïve generalised social anxiety disorder	10 (10/0)	20–33	400 mg CBD of gelatin capsules (with powder CBD dissolved in corn oil)	One single dose	/	VAMS SPECT	Significant reduction of subjective anxiety in CBD group Functional activity changes in limbic and paralimbic cerebral regions in CBD group No side effects
Bergamaschi *et al.* (2011)	Double-blind, randomised, placebo-controlled, clinical trial	Treatment-naïve generalised social anxiety disorder	12 (6/6) CBD group 12 (6/6) place group 12 (6/6) HC		600 mg CBD in gelatin capsules (with powder CBD dissolved in corn oil)	One single dose	/	VAMS SSPS BSS	Significant reduction of anxiety symptoms, cognitive impairment and speech performance discomfort in CBD group
Zuardi *et al.* (2010)	Case report	Bipolar disorder type I, manic episode with psychotic features	2 (0/2)	25 17	600 mg CBD (up to 1200 mg/day)	25 days	Olanzapine during the first 2 weeks	BPRS YMRSUKU	No significant symptoms improvements with CBD. No side effects
Crippa *et al.* (2013)	Case report	Cannabis dependence and cannabis withdrawal syndrome	1 (0/1)	19	300 up to 600 mg on in gelatin capsules (with powder CBD dissolved in corn oil)	10 days	/	WDSM WSC BAI BDI	Reduction of withdrawal, anxiety and dissociative symptoms No significant effect on long-term cannabis dependence
Shannon and Opila-Lehman (2015)	Case report	Cannabis dependence, bipolar disorder	1 (1/0)	27	18 up to 24 mg CBD oil	Prolonged over time	/	PSQI HAM-A	CBD was effective in quitting cannabis abuse, in reducing anxiety symptoms and improving quality of life

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Table 1. *Continued*

Article	Study design	Diagnosis	Sample (M/F)	Age (years old)	CBD dosage/ formulation	CBD timing	Augmentation	Scales, test and measurements	Main results
Morgan *et al.* (2013)	Double-blind, randomised, placebo-controlled clinical trial	Tobacco use disorder	18 (12/6) CBD group 12 (6/6) placebo group	18–35	CBD (400 μg dose for each depress of the solution aerosol in the inhaler) via a pressurised metered dose inhaler	1 week	/	STAI BDI BIS	Significant reduction of cigarettes smoked in CBD group. No significant effects on craving. No side effects

BACS, Brief Assessment of Cognition in Schizophrenia; BAI, Beck Anxiety Inventory; BARS, Barnes Akathisia Rating Scale; BDI, Beck Depression Inventory; BIS, Behaviour Impulsivity Scale; BPRS, Brief Psychiatric Rating Scale; BSS, Bodily Symptoms Scale; CBD, cannabidiol; CGI, Global Clinical Impression Scale; EPS, Extrapyramidal Symptoms Rating Scale; FAAH, fatty acid amide hydrolase; FAB, Frontal Assessment Battery; GAF, Global Assessment of Functioning; Hamilton Anxiety Rating Scale; HC, healthy controls; IOPSI, Interactive Observation Scale for Psychiatric Inpatients; MCCB, Matrix Consensus Cognitive Battery; MMSE, Mini-Mental Status Examination; MWSC, Marijuana Withdrawal Symptom Checklist; NIA, no information available; PANSS-N, Negative Subscale of Positive and Negative Syndrome Scale; PPQ, Parkinson Psychosis Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SANS, Scale for Assessment of Negative Symptoms; SAS, Social Anxiety Scale; SAS, Simpson-Angus Scale for Parkinson; SCWT, Stroop Color-Word Test; SKZ, schizophrenia; SPECT, single-photon emission computer tomography; SPSS, Self-Statements during Public Speaking Scale; STAI, Spielberger Trait Anxiety Inventory; UKU, UKU Side Effect Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; VAMS, Visual Analogue Mood Scale; WDS, Withdrawal Discomfort Score; YMRS, Young Mania Rating Scale.

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research group, in patients diagnosed with generalised social anxiety disorder (SAD) (Bergamaschi *et al.* 2011; Crippa *et al.* 2011). Interestingly, the authors showed that a single dose of CBD not only significantly decreased subjective anxiety symptoms (Crippa *et al.* 2011), but also reduced cognitive impairment, speech performance discomfort and alert in anticipatory speech during a Simulation Public Speaking Test (Bergamaschi *et al.* 2011), in comparison to the placebo group.

In this regard, the anxiolytic effect exerted by CBD has been mainly related to its agonist activity towards serotonin type 1A (5HT1A) receptors (Soares & Campos, 2017) in specific cerebral areas, including the dorsal periaqueductal grey, the bed nucleus of the stria terminalis and the medial prefrontal cortex (Campos *et al.* 2012). Specifically, even if the exact agonist mechanism is still unclear, some authors proposed that CBD may activate 5HT1A receptors by increasing guanosine-5′-triphosphate binding to G_i protein and by reducing cyclic adenosine monophosphate concentration, similarly to the serotonin neurotransmitter (Russo *et al.* 2005). Moreover, the acute anxiolytic effect of CBD has also been related to its capacity to modify cerebral blood flow in brain sites typically involved in anxiety, such as amygdala, hippocampus, hypothalamus and cingulate cortex (Soares & Campos, 2017). In this perspective, Crippa *et al.* (Crippa *et al.* 2011) performed a cerebral single-photon emission computed tomography scan in ten patients with SAD before and after acute CBD or placebo administration. Interestingly, the authors showed that while a reduced regional cerebral blood flow in left parahippocampal gyrus, hippocampus and inferior temporal gyrus was detected among the patients taking CBD, an increased radiotracer uptake was found in the right posterior cingulate gyrus in the same group.

In conclusion, these findings suggest that, in patients with SAD, CBD may exert an acute anxiolytic effect when administered in a single high dose. Remarkably, this effect may be mainly related to the capacity of CBD to suddenly modify cerebral blood flow in limbic and paralimbic areas (Crippa *et al.* 2011) and to agonise 5HT1A receptors (Bergamaschi *et al.* 2011).

CBD and substance abuse disorder

The pharmacological effects of CBD have also been tested in the treatment of substance abuse disorder by three studies. The case report carried out by Crippa *et al.* (Crippa *et al.* 2013) found that a 10 days oral administration of CBD may acutely reduce withdrawal, anxiety and dissociative symptoms in a patient with cannabis dependence who previously failed to quit cannabis consumption due to serious abstinence symptoms. However, the authors showed that 10 days treatment with CBD was not effective to interrupt long-term relapses of cannabis abuse (Crippa *et al.* 2013). In contrast, in a subsequent case report, Shannon and Opila-Lehman (Shannon & Opila-Lehman, 2015) reported that a prolonged administration of CBD to one BD patient with cannabis dependence not only reduced anxiety symptoms and ameliorate overall quality of life, but also prevented the patient from resuming cannabis consumption. Finally, a potential role of CBD in the treatment of tobacco use disorder has been suggested by the only one double-blind randomised controlled clinical trial performed by Morgan *et al.*, who showed that the CBD group significantly decreased the number of cigarettes smoked without, though, exhibiting any specific beneficial effects on craving symptoms, compared with the placebo group (Morgan *et al.* 2013).

Overall these results might be explained considering that long-term cannabis consumption has been linked to a progressive desensitisation and downregulation of CB1R, which, in turn, may cause the onset of withdrawal symptoms when the substance is missing (Bonnet & Preuss, 2017). Therefore, the capacity of CBD to reduce substance-induced withdrawal symptoms has been attributed to its ability to acutely antagonise CB1R and to chronically enhance the physiological endocannabinoid neurotransmission (Prud'Homme *et al.* 2015). With regards to tobacco addiction, the inhibition of acid amide hydrolase induced by CBD has been hypothesised to reduce the reinforcing effects of nicotine (Morgan *et al.* 2013). Additionally, the agonist activity of CBD towards 5HT1A receptors may also contribute to the anti-craving effect of CBD and to reduce the relapses of substance abuse by regulating drug reward system, anxiety symptoms and stress management (Prud'Homme *et al.* 2015). Finally, CBD may regulate the glutamatergic signalling through modulation of serotoninergic and endocannabinoid systems and this mechanism may also have a role in the treatment of addictive behaviours (Rodríguez-Muñoz *et al.* 2016), since a dysregulation of glutamatergic transmission has been widely related to both drug-seeking behaviours and abuse relapses (Prud'Homme *et al.* 2015).

These evidences suggest that acute administration of CBD may reduce withdrawal symptoms of cannabis dependence (Crippa *et al.* 2013), but the treatment needs to be prolonged over time in order to help quitting cannabis (Shannon & Opila-Lehman, 2015) or tobacco use (Morgan *et al.* 2013). The efficacy of CBD in the treatment of addictive disorders has been mostly hypothetically linked to the modulation of endocannabinoid, serotoninergic and glutamatergic systems.

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CBD and cognitive impairment in psychiatric patients

As regards to neuropsychological functioning, three studies have considered the pro-cognitive effects of CBD in psychotic patients (Hallak *et al.* 2010; Boggs *et al.* 2018; McGuire *et al.* 2018). A single oral dose (Hallak *et al.* 2010) or a 6-week oral administration (Boggs *et al.* 2018) of CBD were not more effective than placebo in ameliorating cognitive performances among outpatients with SKZ. In contrast, McGuire *et al.* (McGuire *et al.* 2018) detected a trend of higher enhancement, although not statistically significant, in cognitive performance and overall functioning in patients with SKZ treated with oral CBD for 6 weeks in adjunction to their ongoing antipsychotic medications.

As a whole, these findings are not surprising, especially because preclinical studies attributed the potential role of CBD in the treatment of cognitive impairment to its capacity to reduce both inflammatory state and oxidative stress as well to promote neurogenesis by increasing brain-derived neurotrophic factor levels (Osborne *et al.* 2017). Finally, the activity of CBD towards 5HT1A and adenosine A2A receptors may also contribute to improve cognitive performances (Osborne *et al.* 2017).

Therefore, it may be speculated that CBD pro-cognitive effects may need longer time of administration in order to detect significant cognitive enhancement, since acute or long-term CBD administration within 6 weeks seemed to not significantly improve cognitive functioning in SKZ patients (Hallak *et al.* 2010; Boggs *et al.* 2018; McGuire *et al.* 2018).

Conclusions

In conclusion, the so far investigated mechanisms of action of CBD may likely explain the preliminary evidences of efficacy in the treatment of psychiatric disorders, especially in psychotic, anxiety and substance-induced disorders. However, the findings presented in this literature overview must be considered in light of some limitations. First, there are still few randomised placebo-controlled clinical trials with small sample size. Second, CBD was administered in inconsistent dosage, formulation and timing of administration. Third, some studies tested CBD efficacy in adjunction to standard medications (Zuardi *et al.* 1995, 2009, 2010; Leweke *et al.* 2012; Boggs *et al.* 2018; McGuire *et al.* 2018), which may have therefore conditioned the results. Fourth, major considerations must be given to the lack of assessment of biological measures among the above-mentioned studies, since only three studies evaluated biological measures, such as endocannabinoid (Leweke *et al.* 2012) or CBD plasma levels (McGuire *et al.* 2018) and cerebral blood flow changes (Crippa *et al.* 2011).

Nonetheless, all together, such preliminary evidences suggest that CBD may have an effective therapeutic role in the treatment of psychiatric disorders. However, further and larger randomised placebo-controlled clinical trials studies should be performed considering not only the clinical outcomes of CBD administration, but also its effect on biological parameters such as neurotransmitter signalling, pharmacokinetics, structural and functional cerebral modifications. This approach may help to clarify the wide spectrum of action of this new molecule in psychiatric disorders.

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