THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY, 2017
http://dx.doi.org/10.1080/15622975.2017.1285049

ORIGINAL INVESTIGATION

Is there a role for cannabidiol in psychiatry?

Julia Machado Khoury[a,b], Maila de Castro Lourenço das Neves[a], Marco Antônio Valente Roque[a], Daniela Alves de Brito Queiroz[a], André Augusto Corrêa de Freitas[a], Ângelo de Fátima[c], Fabrício Moreira[d] and Frederico Duarte Garcia[a,b,e,f]

[a]Department of Mental Health, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil; [b]Postgraduation Program in Molecular Medicine, School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil; [c]Department of Chemistry, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil; [d]Department of Pharmacology, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil; [e]INCT de Medicina Molecular, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil; [f]Unité Inserm U1073, Rouen, France

ABSTRACT

Objectives: Understanding whether cannabidiol (CBD) is useful and safe for the treatment of psychiatric disorders is essential to empower psychiatrists and patients to take good clinical decisions. Our aim was to conduct a systematic review regarding the benefits and adverse events (AEs) of CBD in the treatment of schizophrenia, psychotic disorders, anxiety disorders, depression, bipolar disorder and substance-use disorders.

Methods: We conducted a literature search in PubMed, Scielo, and Clinicaltrials.gov databases. Evidence was classified according to the WFSBP task forces standards.

Results: Bibliographic research yielded 692 records. After analysis, we included six case reports and seven trials, comprising 201 subjects. Most the studies published presented several drawbacks and did not reach statistical significance. We have not found evidence regarding major depressive and bipolar disorders. The level of evidence for cannabis withdrawal is B; cannabis addiction is C2; treatment of positive symptoms in schizophrenia and anxiety in social anxiety disorder is C1. Discrete or no AEs were reported. The most frequently reported AEs are sedation and dizziness.

Conclusion: The evidence regarding efficacy and safety of CBD in psychiatry is still scarce. Further larger well-designed randomised controlled trials are required to assess the effects of CBD in psychiatric disorders.

ARTICLE HISTORY
Received 5 September 2016
Revised 12 December 2016
Accepted 16 January 2017

KEYWORDS
Cannabidiol; pharmacotherapy; psychiatry; adverse effects; psychiatric disorders

Introduction

A growing body of research on the endocannabinoid system (ECS) and phytocannabinoids has been produced in the last 20 years (Di Marzo & Piscitelli 2015; Khoury et al. 2016; Ligresti et al. 2016).

The ECS comprises endogenous cannabinoids (e.g., anandamide and 2-archydonioilglycerol), cannabinoid receptors type 1 (CB1) and 2 (CB2) and the enzymes responsible for synthesis and degradation of endocannabinoids. CB1 receptors are abundant in the central nervous system (CNS), particularly in the cortex, basal ganglia, hippocampus and cerebellum. CB2 receptors are expressed primarily in the immune and gastrointestinal systems and are also present in neurons, microglia and vascular elements of the CNS (Lu & Mackie 2016).

Cannabinoids have emerged as a new class of drugs with potential effects over a broad range of neurological and psychiatric disorders (Campos et al. 2016). Phytocannabinoids are terpenophenolic molecules derived from the *Cannabis sativa* plant (Campos et al. 2016). Δ-9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most concentrated substances found in *Cannabis* extracts (Mechoulam et al. 1965) and the most widely studied. Unlike THC, CBD does not cause psychotomimetic, cognitive or motor effects in humans, and in pre-clinical models CBD acts as a partial agonist of cannabinoid receptors CB1 and CB2 (Pertwee 2005).

The action of CBD in psychiatric disorders is not completely understood. Some effects of CBD seem to be induced by its agonistic effect on the CB1 receptor, although CBD may also antagonise CB1 receptors agonists (Pertwee et al. 2002). Given the low affinity of CBD for CB1 and CB2 receptors, it probably acts through inhibition of hydrolysis or reuptake of

CONTACT Frederico Garcia fredgarcia@ufmg.br Departement of Mental Health, Federal University of Minas Gerais (UFMG), Avenida Alfredo Balena, 190, Sala 240, CEP 30130-100, Belo Horizonte, MG, Brazil

anandamide, which may facilitate endocannabionoid-mediated neurotransmission (Bisogno et al. 2001; Bitencourt et al. 2008; Gomes et al. 2011; Leweke et al. 2012). Recent studies have reported that CBD inhibits the anandamide agonistic effects in CB1 and CB2 receptors, and has antioxidant and neuroprotective effects (Campos et al. 2016). Moreover, Laprairie et al. (2015) demonstrated that CBD also acts as a non-competitive negative allosteric modulator of CB1 receptors. These authors suggest that this allosteric modulation, in concurrence with effects not mediated by CB1 receptors, may be responsible for the in vivo effects of CBD.

The research of possible therapeutic actions of CBD started in the 1970s (Karniol et al. 1974). CBD seems to produce a broad spectrum of potential therapeutic properties in animal models and human pre-clinical and clinical studies, notably antiepileptic, sedative, anxiolytic, antipsychotic, antidepressant and neuroprotective effects (Bergamaschi et al. 2011; Campos et al. 2016). The mechanisms yielding such effects in psychiatric disorders are not completely understood.

The favourable evidence on the use of CBD for the treatment of some types of epilepsy (Devinsky et al. 2016; GW Pharmaceuticals 2016) resistant to usual therapies, mainly those types caused by rare metabolic syndromes, has fostered a significant debate among the medical community in the last few years. Some countries, such as the UK, Canada, the Netherlands and some states in the United States authorised the use of CBD formulations for the treatment of epilepsy resistant to other medications (Whiting et al. 2015). In 2014, the Brazilian Federal Council of Medicine (FCM) approved the compassionate use of CBD for the treatment of children and adolescents with epilepsy resistant to usual treatments (Conselho Federal de Medicina 2014). Compassionate use corresponds to the prescription of a new drug, not yet registered by National Agency for Sanitary Surveillance (Anvisa), for patients who have severe disease and did not respond to drugs registered in the country. Moreover, the FCM authorised only neurologists, neurosurgeons and psychiatrists to prescribe CBD in these conditions and prohibits the prescription of *Cannabis* in natura for medical use.

Understanding whether CBD is a useful and safe treatment of psychiatric disorders is essential to empower psychiatrists and patients to make good clinical decisions. In this study, we performed a systematic literature review regarding therapeutic effects, adverse effects (AEs) and long-term safety of CBD for the treatment of patients with psychiatric disorders. Our primary goal was to assess clinical evidence evaluating the use and clinical safety of CBD for the treatment of schizophrenia, psychotic disorders, anxiety disorders, depression, bipolar disorder and substance-use disorders.

Methods

Search strategy

We conducted a literature search in PubMed, Scielo and Clinicaltrials.gov databases. The search was restricted to the English language and articles before August 2016. The following Medical Subject Headings (MeSH) terms were used in the search: ('cannabidiol') AND ('anxiety' OR 'psychosis' OR 'schizophrenia' OR 'depression' OR 'bipolar disorder' OR 'addiction' OR 'substance-use disorder'); and ('cannabidiol') AND each of the above-mentioned disorders uniterms. Two reviewers independently searched the titles and abstracts, carefully reading full complete articles, when relevant.

Eligibility criteria

To be included the studies had to assess the outcomes of CBD in the treatment of anxiety, psychosis, schizophrenia, depressive disorder, bipolar disorder or substance-use disorders. All types of study design were included: clinical trials (randomised or not), observational, retrospective and prospective studies, and case reports. We excluded pre-clinical, expert opinions, literature reviews and research not regarding psychiatric disorders.

Data extraction and analysis

When available, the following data were retrieved from the included studies: (1) Reference; (2) Study design; (3) Participant profile; (4) Sample size; (5) Primary goals; (6) Intervention type; (7) Results; and (8) Main limitations.

Aiming to achieve a uniform and appropriate ranking of a hierarchy of evidence we used the level of evidence level previously utilised by the World Federation of Societies of Biological Psychiatry (WFSBP) task forces. In brief, Grade 'A' corresponds to 'Full evidence from controlled studies'; Grade 'B', 'Limited positive evidence from controlled studies'; Grade 'C', 'Evidence from uncontrolled studies or case reports/expert opinion', this grade is subdivided in 'C1' Uncontrolled studies; 'C2' Case reports and 'C3' Opinion of experts in the field or clinical experience; Grade 'D', 'Inconsistent results'; Grade 'E', 'Negative

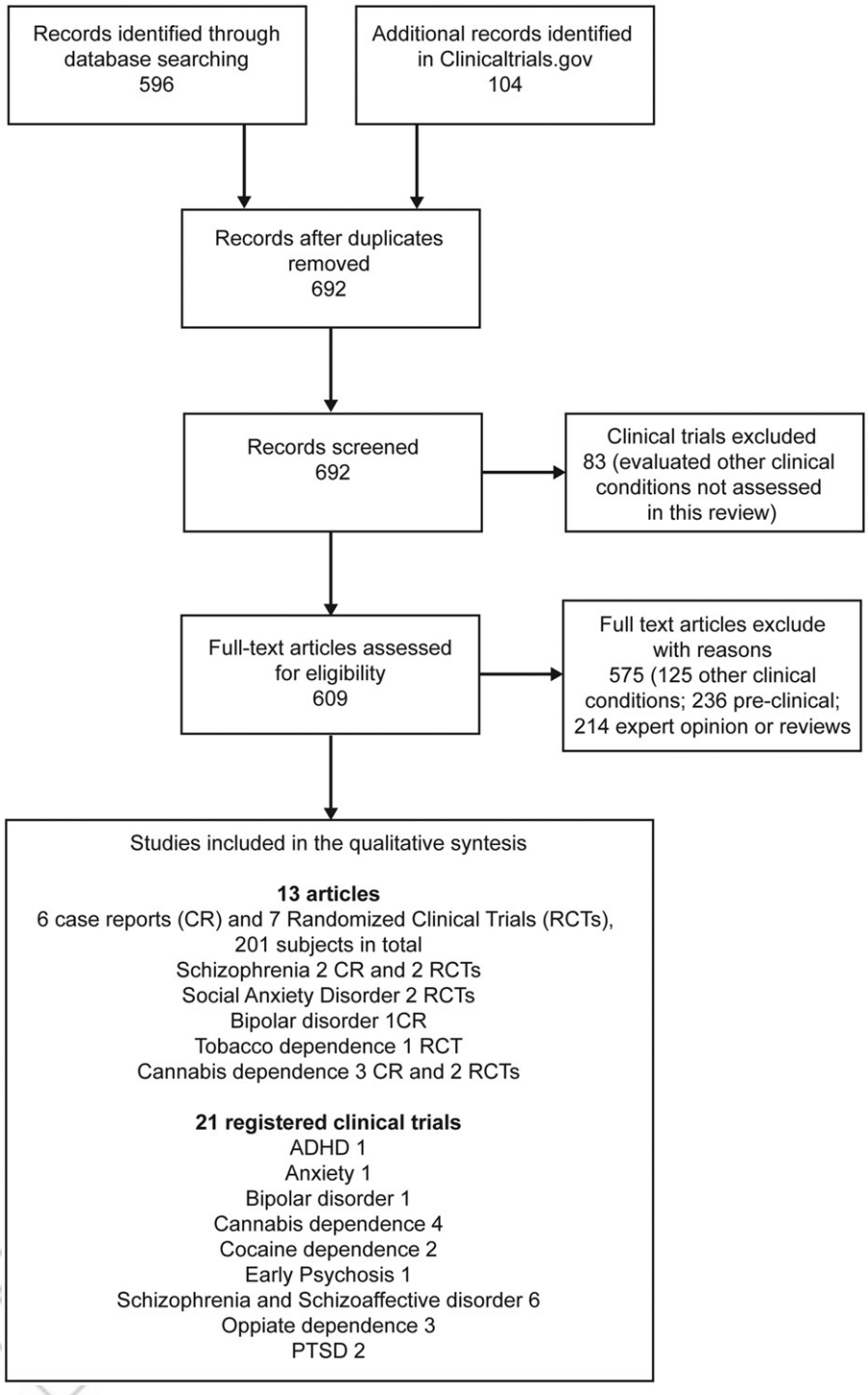

Figure 1. Bibliographic flow diagram.

Evidence' or Grade 'F', 'Lack of evidence'. For more details refer to Bandelow et al. (2008).

Results

In the flow diagram (Figure 1), the quantitative results of the bibliographic search are shown. We identified 596 papers and 104 registered clinical trials using CBD as a treatment. After careful selection, we included in the analysis 21 registered clinical trials and 13 articles. We excluded 83 registered clinical trials because they evaluated other clinical conditions not assessed in this review; and another 583 papers (125 because they regarded other clinical conditions; 236 because they were pre-clinical studies; 214 because they were

expert opinions or reviews; and eight because they were duplicated).

We summarised the results in Tables 1 and 2. In the folowing, we describe the studies according to the disorder treated and by the quality of evidence.

CBD formulations used in the studies

Four oral formulations of CBD are described and utilised in the studies included in the analysis. First, an oral formulation consisted of CBD powder dissolved in oil, in doses of 200, 400, 600 and 800 mg. The second formulation was a controlled release (CR) presentation, named Cannabidiol CR (Arvisol®, Echo Pharmaceuticals B.V., Netherlands) in a dose of 320 mg. The third is an orally bioavailable combination of THC/CBD (2.7:2.5 mg/spray), used as buccal sprays, commercially named Sativex® (GW Pharmaceuticals, Cambridge, UK). Some countries have already approved this formulation for the treatment of spasticity due to multiple sclerosis (Whiting et al. 2015). The fourth is a buccal spray of CBD diluted in alcohol.

Schizophrenia and psychosis

The involvement of the ECS in psychosis was first evoked by epidemiological studies associating the use of cannabis with an increased risk of developing schizophrenia (Gururajan & Malone 2016). Morgan & Curran (2008) quantified THC and CBD in the hair of 140 cannabis users. The THC-only users group showed higher levels of positive schizophrenia-like symptoms when compared to the groups without cannabinoids in hair as well as subjects presenting THC and CBD. Schubart et al. (2011) found a significant inverse relationship between CBD drug content and self-reported positive schizophrenia-like symptoms in a sample of 1887 cannabis users.

Also, Leweke et al. (1999) reported increased levels of anandamide in the cerebrospinal fluid of patients with schizophrenia, evoking a neurobiological role of the ECS in schizophrenia. Despite the positive results on the use of antagonists of CB1 in animals, Meltzer et al. (2004) have not found significant effects of CB1 antagonist/inverse agonist (e.g., rimonabant) on symptoms or AEs in a randomised controlled trial (RCT) including 72 patients with schizophrenia.

CBD produced an antipsychotic effect in pre-clinical studies and in models of psychosis in healthy subjects (Leweke et al. 2016). In animal models, CBD presents an antipsychotic profile similar to atypical antipsychotics such as clozapine. Like clozapine, CBD attenuates dopaminergic effects linked to apomorphine and reduces hyperactivity induced by amphetamine and ketamine in mice (Moreira & Guimaraes 2005); CBD activates neurons in mesolimbic areas but not in motor control areas (Guimaraes et al. 2004); CBD reverses gating deficits induced by NMDA receptor antagonists (Gomes et al. 2014; Pedrazzi et al. 2015).

Winton-Brown et al. (2011) reported that 300 or 600 mg of CBD prevented psychotic symptoms induced by 10 mg of THC. In a second study using a similar strategy, Englund et al. (2013) reported that pre-treatment with 600 mg of CBD inhibited THC-elicited psychosis and cognitive impairment, but the result was not statistically significant. On another hand, Hallak et al. (2011) reported that CBD did not attenuate the behavioural and psychotic effects of ketamine, in a sample of 10 healthy subjects receiving ketamine and 600 mg of CBD during 1 week.

Moreover, patients with schizophrenia present elevated levels of anandamide and modifications in the expression of cannabinoid receptors in several brain regions (Leweke et al. 1999; Eggan et al. 2008), suggesting that ECS may be involved in the pathophysiology of this disorder. Genetic and animal model evidence suggest a link between CB2 receptors and an increased risk for schizophrenia (Bae et al. 2014). Neuroimaging studies demonstrated that THC and CBD can have opposite effects on regional brain function, suggesting that CBD may block psychotic symptoms (Bhattacharyya et al. 2009).

Hence, the rationale to use CBD in the treatment of patients with schizophrenia is based on the findings that THC-rich cannabis accentuates and that CBD-rich cannabis may decrease psychotic and cognitive symptoms (Zuardi et al. 1995; Morgan & Curran 2008; Bhattacharyya et al. 2010; Morgan et al. 2012).

We found five registered clinical studies assessing the use of CBD in the treatment of schizophrenia on the site ClinicalTrials.gov. Three studies were assigned as completed and two as recruiting. We found the published results of two of the completed studies. All trials used a CBD powder dissolved in oil formulation in doses varying from 200 to 800 mg.

The initial search on PubMed issued 77 papers, after data search we included four studies in analysis and excluded 41 reviews or expert opinions, eight studies on other disorders and 24 pre-clinical studies. The two case reports and the two RCTs assessing the use of CBD in patients with schizophrenia are described below.

Zuardi et al. (1995) described a case report of a 19-year-old female patient with treatment-resistant schizophrenia (TRS). After a washout period of 4 days, she received CBD titrated up to 1500 mg/day in

Table 1. Trials included in the analysis regarding the clinical trials evaluating CBD efficacy and adverse effects in the treatment of psychiatric disorders. Data are organised according to the main disorder treated.

Disorder	References	Study design	Participants profile	Sample size	Main goals	Intervention type	CBD formulation	Dose	Results	Main Limitations
Schizophrenia	Zuardi et al. (1995)	Case report	19-years-old inpatient female with TRS	1	Report a case	Four days' washout, CBD up to 1500mg/day during four weeks	CBD powder in oil	1500mg/day	Improvement of symptoms	N/A
	Zuardi et al. (2006)	Case report	22-yr-old male inpatients with TRS	3	Report a case	Five days washout, CBD 40 mg-1280mg/day in monotherapy, during 4 weeks	CBD	40mg up to 1280mg/day	Mild Improvement in one patient. Good tolerability	N/A
	Leweke et al. (2012)	Double-blind RCT	Subjects with acute schizophrenia	42	Assess non-inferiority of CBD compared to amisulpride	Three days washout; CBD or amisulpride 200mg/day titrated up to 800mg/day	CBD	200mg up to 800mg/day	Equivalent response of CBD and amisulpride on reduction of PANSS and BPRS at day 14 and 28	Underpowered sample
	Leweke et al. (2013)	Double-blind RCT	Early psychosis	29	Compare efficacy of CBD and placebo in the reduction of psychotic symptoms	Crossover of treatments after 14 days	CBD	600 mg/day	No statistical difference between CBD and placebo in PANSS	Small sample, short duration of active treatment, carry-over effects
Generalised Social Anxiety disorder	Crippa et al. (2011)	Double-blind RCT	Students diagnosed with generalised social anxiety disorder	10	Compare anxiolytic effects between CBD and placebo	Single CBD intake before a SPECT scanning, simulating the anxiety-evoking procedure	CBD powder in oil	400 mg	CBD significantly reduced subjective anxiety and ECD uptake	Small sample, extrapolated anxiogenic stimuli
	Bergmaschi (2011)	Double-blind RCT	Students diagnosed with generalised social anxiety disorder	24	Compare anxiolytic effects between CBD and placebo	Single CBD intake before simulation public speaking test	CBD powder in oil	600 mg	CBD significantly reduced anxiety, cognitive impairment and discomfort	N/A
Bipolar disorder	Zuardi et al. (2010)	Case report	Females with bipolar disorder	2	Report a case	Five days washout, CBD 1200mg in monotherapy for 24 days, then placebo 5 days and olanzapine.	CBD powder in oil	1200 mg	No improvement	N/A
Tobacco dependence	Morgan et al. (2013)	Double-blind RCT	Smokers recruited	24	Assess the impact of ad-	One week use of CBD on an	CBD 5% in absolute alcohol	400 mcg/dose in as-needed	Reduction of 40% of	No biochemical assays of

(*continued*)

Table 1. Continued

Disorder	References	Study design	Participants profile	Sample size	Main goals	Intervention type	CBD formulation	Dose	Results	Main Limitations
			from the community		hoc use of CBD in smokers wishing to quit smoking	as-needed basis	in pressurised metered dose inhaler	basis	smoked cigarettes in CBD group. No effects on craving	nicotine metabolites, results based solely in self-reports
Cannabis dependence	Crippa et al. (2013)	Case report	19-years-old female with cannabis withdrawal syndrome	1	Report a case	Hospitalization. Oral CBD 300mg on Day 1; 600mg days 2-10 and 300mg in day 11.	CBD	300 mg to 600mg	Fast and progressive decrease in cannabis withdrawal, anxiety and dissociative symptoms	N/A
	Shannon and Opila-Lehman (2015)	Case report	27-years-old male with cannabis dependence and bipolar disorder	1	Report a case	24 to 18 mg of CBD once a day	CBD-rich oil	18-24 mg	Interruption of cannabis use and decrease in anxiety	N/A
	Trigo et al. (2016)	Case report	Subjects with cannabis dependence	4	Open-label pilot study	12 week use of self-titrated Sativex® and CBT + motivational therapy	Sativex®	Up to 42 sprays/day	Reduction in cannabis use	Lack of control group
	Allsop et al. (2014)	Double-blind RCT	Inpatients with cannabis dependence	51	Compare CBD and placebo in cannabis withdrawal	6-day treatment with Sativex and psychosocial intervention	Sativex®	80 mg/day	Reduction in cannabis withdrawal symptoms and craving. Increased treatment retention	Inpatient setting, sample size
	Trigo et al. (2016)	Double-blind RCT	Subjects with cannabis dependence	9	Compare fixed doses, to self-titrated doses and placebo in cannabis withdrawal symptoms	Eight-week treatment with fixed high doses of CBD or self-titrated CBD or placebo	Sativex®	100 mg/day or up to 108mg/day	Less withdrawal with fixed doses then placebo or self-titrated doses. No adverse effects	Small sample size, lack of standardisation of dosing, short duration of the study

BPRS, Brief Psychiatric Rating Scale; CBD, cannabidiol; PANSS, Positive and Negative Syndrome Scale; RCT, randomised clinical trial; SATIVEX®, Δ9-tetrahydrocannabinol/cannabidiol combination in a buccal spray; TRS, treatment-resistant schizophrenia; THC, Δ-9-tetrahydrocannabinol.

Table 2. Registered clinical trials included in the analysis regarding the clinical trials evaluating CBD efficacy and adverse effects in the treatment of psychiatric disorders. Data are organised according to the main disorder treated.

Main disorder	Clinical trial id	Title	Medication	Dose	Comparator	Design	Phase	Status	Outcome
Anxiety	NCT02548559	Sublingual CBD for Anxiety	CBD (tincture)	28,8mg	N/A	Open label	I	Not recruiting	Self-Reported Anxiety as Assessed by the Beck Anxiety Inventory
Bipolar Disorder	NCT00397605	Cannabinoids in Bipolar Affective Disorder	THC:CBD (Standardised plant extract)	01:01	Placebo	RCT	N/A	Withdrawn prior to enrolment	Mood ratings will be performed weekly
Cannabis Dependence	NCT01748799	Fixed or Self-Titrated Dosages of Sativex on Cannabis Users	SATIVEX®	up to 40 sprays/ day (108mg THC)	Placebo	RCT	II	Completed	Feasibility (number of patients completing the study)
	NCT01747850	Sativex and Behavioural-relapse Prevention Strategy in Cannabis Dependence	SATIVEX®	up to 42 sprays/ day (108mg THC)	Placebo	RCT	II	Completed	Tolerability and efficacy
	NCT02044809	Cannabidiol: a Novel Intervention for Cannabis Use Problems?	CBD; Cannabidiol CR (Arvisol); Placebo; Antipsychotics	200 and 400mg and 800mg	Placebo	RCT	II a/b	Recruiting	Number of days abstinent from cannabis (Metabolites in urine)
	NCT02777502	Effects of Cannabidiol on Marijuana-seeking in Humans	CBD	N/A	N/A	Observational	0	Recruiting	Marijuana Craving Visual Analogue Scale
Cannabis Withdrawal	NCT02083874	Cannabidiol (CBD) for the Management of Cannabis Withdrawal: A Phase II Proof of Concept Study	CBD	300mg	N/A	Single group	II	Unknown	Severity of cannabis withdrawal
Cocaine Craving	NCT02559167	Cannabidiol and Cocaine Craving/Dependence (CBD)	CBD	800mg	Placebo	RCT	II	Not recruiting	Drug-cue-induced craving
Opiate Dependence	NCT01605539	Acute and Short-term Effects of Cannabidiol Administration on Cue-induced Craving in Drug-abstinent Heroin Dependent Subjects	CBD	400 and 800 mg	Placebo	RCT	II	Ongoing	Visual Analogue Scale for Craving (VASC)
	NCT02539823	Acute and Short-term Effects of CBD on Cue-induced Craving in Drug-abstinent Heroin dependent Humans	CBD	200 and 400mg and 800mg	Placebo	RCT	II	Recruiting	Cue-Induced In-Clinic Craving
	NCT01311778	Study to Test the Safety and Efficacy of Cannabidiol as a Treatment Intervention for Opioid Relapse	CBD 400 mg will receive 400 mg of CBD in two test sessions along with 0.5 mcg/kg and 1mcg/kg of fentanyl	400 and 800 mg	Placebo	RCT	I	Completed	Safety of CBD oral administration prior to fentanyl IV administration

(*continued*)

Table 2. Continued

Main disorder	Clinical trial id	Title	Medication	Dose	Comparator	Design	Phase	Status	Outcome
PTSD	NCT02517424	Evaluating Safety and Efficacy of Cannabis in Participants With Chronic Posttraumatic Stress Disorder	Cannabis	Different proportions of THC/CBD	Placebo	RCT	II	recruiting	Clinician Administered PTSD Scale
	NCT02759185	Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With Chronic, Treatment-Resistant PTSD	High CBD smoked marijuana			RCT	II	Not recruiting	Clinician Administered PTSD Scale Global Severity Score
Schizophrenia or Schizoaffective disorder	NCT02051387	Cannabidiol as a Different Type of an Antipsychotic: Drug Delivery and Interaction Study (CBD-IS)	CBD; Cannabidiol CR (Arvisol®); Placebo; Antipsychotics	200mg	Placebo	RCT	I	Recruiting	Serum antipsychotic concentration
	NCT00916201	Evaluation Study of New Compounds With Potential Use in Schizophrenia (EICAS)	Cannabidiol CR	320mg			I	Not recruiting	Clinical assessment with several psychopathological scores for self-assessment and peer evaluation
	NCT02088060	A Four-week Clinical Trial Investigating Efficacy and Safety of Cannabidiol as a Treatment for Acutely Ill Schizophrenic Patients	CBD tablets 300 mg twice a day and placebo olanzapine capsule once a day over 4 weeks	300mg	Placebo	RCT	II	Recruiting	PANSS
	NCT00309413	A Clinical Trial on the Antipsychotic Properties of Cannabidiol	CBD and placebo	600mg	Placebo	RCT		completed	BPRS
	NCT00588731	Cannabidiol Treatment of Cognitive Dysfunction in Schizophrenia	CBD	N/A	Placebo	RCT	II	Completed	Verbal short-term memory (Time Frame: 6 weeks)
	NCT00628290	Evaluation of the Antipsychotic Efficacy of Cannabidiol in Acute Schizophrenic Psychosis (CBD-CT1)	CBD; amisulpride	200mg			II	completed	PANSS
Early Psychosis	NCT02504151	Cannabidiol Treatment in Patients With Early Psychosis (CBD)	CBD	800mg	Placebo	RCT	II	Recruiting	PANSS
ADHD	NCT02249299	Experimental Medicine in ADHD - Cannabinoids (EMA-C)	SATIVEX®	2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD)	Placebo	RCT	N/A	recruiting	Change in performance on the Qb Test

BPRS, Brief Psychiatric Rating Scale; CBD, cannabidiol; IV, intravenous; PANSS, Positive and Negative Syndrome Scale; RCT, randomised clinical trial; SATIVEX®, Δ9-tetrahydrocannabinol/cannabidiol combination in a buccal spray; TRS, treatment-resistant schizophrenia; THC, Δ-9-tetrahydrocannabinol.

Table 3. Summary of evidence levels and recommendation grades accordingly to the disorder. These results should be regarded in the light of the major limitations of the studies detailed in the text.

Disorder	Evidence level	Recommendation grade
Schizophrenia (short term)	C1	4
Generalised social anxiety disorder (Acute)	C1	4
Major depressive disorder	F	N/A
Bipolar disorder	F	N/A
Tobacco addiction	C1	4
Cannabis withdrawal	B	3
Cannabis dependence	C2	4

Grade 'A' corresponds to 'Full evidence from controlled studies'; Grade 'B', 'Limited positive evidence from controlled studies'; Grade 'C', 'Evidence from uncontrolled studies or case reports/expert opinion', this grade is subdivided into 'C1' Uncontrolled studies, 'C2' Case reports and 'C3' Opinion of experts in the field or clinical experience; Grade 'D' 'Inconsistent results'; Grade 'E' 'Negative Evidence'; or Grade 'F' 'Lack of evidence'. For more details refer to Bandelow et al. (2008).

monotherapy during 4 weeks. According to the authors, the patient presented a marked improvement in symptoms, as measured by the Brief Psychiatric Rating Scale (BPRS), and no adverse effects were observed. They also reported symptoms worsening after discontinuation of CBD, even with the use of 12.5 mg of haloperidol.

In a second case report, Zuardi et al. (2006), in an open-label, uncontrolled study, assessed the efficacy of 40 mg CBD titrated up to 1280 mg in monotherapy during 4 weeks, after a washout period of 5 days, in three patients with TRS. The authors reported a mild improvement in one patient and no amelioration of psychotic symptoms in the other two patients. The authors highlighted the good tolerability of CBD in patients with schizophrenia and hypothesised that the short duration of treatment with a therapeutic dose of CBD might have negatively influenced the results of the trial.

Leweke et al. (2012) performed a double-blind RCT to assess whether CBD given for 28 days was non-inferior to amisulpride in the treatment of 42 patients with acute schizophrenia, evaluating treatment results and anandamide levels in serum. After randomisation and a washout period of 3 days, CBD or amisulpride 200 mg/day was titrated up to 800 mg/day and symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) and BPRS at days 14 and 28. The authors reported a comparable reduction of psychotic symptoms with both treatments, although the CBD group had less severe AEs. Moreover, the levels of anandamide were increased in the group treated by CBD, suggesting that higher levels of anandamide may contribute to the antipsychotic effects of CBD. The results should be regarded with consideration for the underpowered sample, as reported by the authors.

In a second trial, Leweke (2013) compared the efficiency of CBD with placebo in a double-blind RCT in a sample of 29 patients presenting first-episode paranoid schizophrenia. The author used a crossover strategy, in which, after randomisation, patients started either CBD 600 mg or placebo and after 14 days were switched to the other treatment. The author reported that CBD significantly improved positive symptoms when compared to baseline, although no statistical difference was found in PANSS between CBD and placebo-treated groups. These results should be considered in light of sample size, short duration of the active treatment and possible carry-over effects.

Four studies assessed the efficacy of CBD on the treatment of schizophrenia: one case report positive (Zuardi et al. 1995) and one negative (Zuardi et al. 2006) for the treatment of patients with TRS. One study found comparable results in symptom reduction between CBD and amisulpride in patients with acute paranoid schizophrenia and schizophreniform psychosis (Leweke et al. 2012). Finally, one study did not identify differences between CBD and placebo in first-episode schizophrenia (Leweke 2013). No information on the long-term effects of CBD on schizophrenia is available.

Considering these results, the category of evidence for short-term treatment of TRS is C1, recommendation grade 4; for first-episode schizophrenia the category of evidence is E.

Anxiety disorders

The potential therapeutic effects of CBD on anxiety disorders have been challenged as it acts on several receptors known to modulate fear- and anxiety-related behaviours, particularly cannabinoid type 1 receptor, the 5-HT_{1a} serotonin receptor, and transient receptor potential vanilloid type 1 (Campos et al. 2012). Preclinical studies have provided evidence on the efficacy of CBD in reducing anxiety behaviours relevant to several disorders without producing further anxiogenic effects (Blessing et al. 2015).

We found one registered clinical trial describing an open-label study assessing the effects of 28.8 mg sublingual CBD in tincture on anxiety measured by the Beck Anxiety Inventory (BAI), without results being described. The bibliographic search issued 104 papers regarding anxiety and CBD; however, we included only six studies (four non-clinical and two clinical) in this analysis, excluding 36 papers regarding pre-clinical

studies, 36 reviews or expert opinions, 19 studies assessing other disorders and seven duplicated papers.

In a seminal study, Zuardi et al. (1982) performed a RCT to evaluate the anxiolytic effects of CBD on the anxiety produced by THC, in a sample of eight healthy subjects. Each volunteer participated in five experimental sessions, separated by a minimum interval of 1 week. In each session, the volunteers received in a double-blind procedure, one of the following oral treatments: THC (0.5 mg/kg); CBD (1 mg/kg); a mixture (0.5 mg/kg THC and 1 mg/kg CBD); placebo and diazepam (10 mg). The primary outcome was measured by the Sielberger's State-trait Anxiety Inventory. The treatments were administered in a different sequence to each volunteer, in such a way that each treatment followed each of the others. The authors reported a significant decrease of THC anxiogenic effect in patients treated simultaneously by THC/CBD and a more prevalent sensation of sleepiness. The small sample size and dose of CBD used in this study should be noted.

Zuardi et al. (1993) also compared the effect of 300 mg of CBD with ipsapirone, diazepam and placebo on subjectively perceived anxiety, measured by a visual analogue mood scale in a double-blind, RCT, using 40 healthy subjects. The authors reported that CBD significantly reduced subjectively perceived anxiety when compared to placebo, without causing sedation like diazepam. The results should be regarded considering the small sample used, a unique use of the medication and the subjective measure of anxiety.

Crippa et al. (2004) evaluated the capacity of 400 mg oral CBD to reduce anxiety induced by neuroimaging procedures, analysing cerebral blood flow in 10 healthy men, in a double-blind, placebo-controlled study. Each subject was assessed on two different occasions, 1 week apart. In the first session, after a 30-min period of adaptation, subjects were given a single dose of oral CBD or placebo. The researchers performed single-photon emission computerised tomography (SPECT) image acquisition 110 min after drug ingestion and subjective ratings on the Visual Analogue Mood Scale (VAMS) 30 min before drug ingestion, at the time of drug ingestion, and at 60 and 75 min afterward. In the second session, an identical procedure was followed except that the other drug was administered. CBD significantly decreased subjective anxiety and increased sedation, while the placebo did not induce significant changes.

Fusar-Poli et al. (2009) performed a crossover study with 15 healthy volunteers. Each subject was imaged with functional magnetic resonance imaging (fMRI) on three separate occasions, with each session preceded by oral administration of THC 10 mg, CBD 600 mg or a capsule of placebo. The results showed that CBD but not THC disrupted forward connectivity between the prefrontal area and subcortical area during the neural response to fearful faces.

Only two clinical studies assessed the use of CBD in patients with anxiety disorders.

Crippa et al. (2011) developed a double-blind, placebo-controlled trial to evaluate the anxiolytic effects of 400 mg of CBD dissolved in corn oil in 10 men diagnosed with a generalised social anxiety disorder (SAD). After taking CBD or placebo, the participants evaluated anxiety by the VAMS 30 min before intake, at drug intake, 60 and 75 min after intake and after SPECT scanning. According to the authors, the medical procedures involved in the SPECT scan corresponded to the anxiety-evoking procedure. CBD significantly reduced subjective anxiety in all endpoints after drug intake and a reduced technetium-99m-ethyl cysteinate diethylester (ECD) uptake in the left parahippocampal gyrus, hippocampus and inferior temporal gyrus, and increased ECD uptake in the right posterior cingulate gyrus.

Bergamaschi et al. (2011) performed a second double-blind trial to compare the effect of 600 mg of CBD dissolved in corn oil with placebo, in a sample of 24 never-treated patients with SAD and 12 healthy controls. The researchers exposed the participants to a simulation public-speaking test (SPTS) and measured anxiety using VAMS and the Negative Self-Statement scale (SSPS-N) in six endpoints during the SPST. The authors reported that CBD significantly reduced anxiety, cognitive impairment and discomfort during speech performance and decreased alert in an anticipatory speech in patients with SAD. The placebo group presented higher anxiety, cognitive impairment, discomfort and alert levels when compared with control group.

Most of the studies assessing the effects of CBD on anxiety confronted healthy subjects to anxiogenic paradigms, but only two studies assessed clinical patients with SAD. Both studies confirmed an effect of CBD administration in reducing acute anxiety in patients with SAD. However, this inference should be considered in the light of the fact that both studies used small samples and did not establish a dose–response correlation between anxiety measurements and CBD plasma levels. Moreover, the studies did not provide information on long-term effects of CBD on this disorder.

Considering these results, the category of evidence for acute anxiety and long-term treatment in SAD by CBD is C1, recommendation grade of 4 and F,

respectively. We have not found studies assessing the effect of CBD on ~~the~~ other anxiety disorders.

Major depressive disorder

Pre-clinical studies suggested that CBD may have an antidepressant action, although their results are incipient, and antidepressant effects may involve CB1 and 5-HT1A receptors (Zanelati et al. 2010; Ashton & Moore 2011; Micale et al. 2013; Linge et al. 2016; Sartim et al. 2016). We found no studies assessing the use of CBD in subjects with major depression in which the primary outcome is antidepressant effect. CBD is considered class F for the treatment of depression.

Bipolar disorder

Anecdotal reports suggested that patients in manic or depressive episodes smoke cannabis to relieve their symptoms. No systematic studies of the use of CBD to treat bipolar disorder exist (Ashton et al. 2005).

Zuardi et al. (2010) described the use of CBD in two cases of female inpatients with bipolar disorder type I. The authors used a crossover methodology after a washout period of 5 days and then CBD 1200 mg/day from the 6th to the 30th day. From the 6th to the 20th day, the first patient, a 34-year-old woman, received adjunctive olanzapine (oral dose of 10–15 mg). On day 31, CBD treatment was discontinued and replaced by placebo for 5 days. The first patient showed symptom improvement while on olanzapine plus CBD but had no additional improvement during CBD monotherapy. The second patient, a 36-year-old woman, had no symptom improvement with any dose of CBD during the trial. One clinical trial was registered but withdrawn before inclusion of patients.

Considering these results, we can classify the evidence on the use of CBD in bipolar disorder as category F, considering the lack of adequate studies proving efficacy or non-efficacy.

Substance-use disorders

The ECS has been associated with neuronal circuits involved in the development of addiction and subsequent drug-seeking behaviours (Sagheddu et al. 2015). The ECS influences acquisition and maintenance of drug-seeking behaviours, playing a role in reward and brain plasticity (Gardner 2005; Heifets & Castillo 2009). Moreover, some studies suggested that CBD is an agonist of ~~5HT1~~$_A$ serotoninergic receptors, regulating stress response and compulsive behaviours (Russo et al. 2005; Gomes et al. 2011; Campos et al. 2012; Breuer et al. 2016). These findings highlight the fact that CBD may be an interesting drug to treat substance-use disorders.

Our search issued nine registered clinical studies regarding the use of CBD in the treatment of substance-use disorders. Five trials were on cannabis dependence, three on opiate addiction and one on cocaine craving treatment. Only one trial on opiate dependence was completed but no data were made available by the researchers. All trials used CBD in powder diluted in oil, except one that used Cannabidiol CR and two that used Sativex®. Only three of these trials were shown as completed with published results.

The initial search, on PubMed, issued 44 articles, after data search we included seven studies in our analysis and excluded 15 reviews or expert opinions, 11 studies on other disorders, nine pre-clinical studies and two repeated papers. The results are reported below according to the target substance treated in the studies.

Tobacco

Only one study assessed the efficacy of CBD on the treatment of nicotine addiction. Morgan et al. (2013) reported a 40% decrease in number of smoked cigarettes among the group of smokers treated with CBD (400 µg/dose inhaled in an as-needed basis) when compared to the placebo in a double-blind RCT with 24 subjects. Both groups presented a reduction in craving on days 1 and 7, but not during follow-up. No further effects on craving or secondary effects were described. Considering this study, the category of evidence for the treatment of tobacco addiction is C1 and recommendation grade of 4.

Cannabis

The treatment of cannabis addiction was described in two case reports. In the first Crippa et al. (2013) reported a 19-year-old female patient with 'heavy' and continued cannabis dependence and a history of cannabis withdrawal syndrome. The patient was hospitalised and treated with oral CBD at a dose of 300 mg on Day 1; 600 mg on Days 2–10 and 300 mg on Day 11. The authors suggested that the treatment produced a fast and progressive decrease in anxious and dissociative cannabis withdrawal symptoms during the first 10 days of cannabis abstinence.

In a second case report, Shannon and Opila-Lehman (2015) prescribed CBD-rich oil and tapered dosage from 24 mg once a day to 18 mg in the single

case of a 27-year-old male subject with cannabis dependence and bipolar disorder. The patient reported the interruption of cannabis use and improvement in anxiety and sleep disorders.

Trigo et al. (2016) reported an open-label pilot study to assess feasibility for a larger RCT. The study was comprised of four subjects with cannabis dependence treated with self-titrated Sativex® (tapered during days 1–10, to a maximum of 42 oromucosal sprays) associated ~~to~~ motivational therapy and cognitive behaviour therapy during a 12-week study; follow-up consisted of weekly visits. The authors reported good tolerability of Sativex® in adults with cannabis dependence, and a reduction in cannabis use among the patients assessed. The main limitation of this study was the lack of a control group.

Allsop et al. (2014) assessed the effects of Sativex® in a two-site RCT, in a sample of 51 inpatients presenting cannabis dependence. During a 6-day study, 24 subjects received placebo and Sativex® (86.4 mg THC and 80 mg CBD) plus a standardised psychosocial intervention. The authors reported that Sativex® treatment significantly reduced the overall severity of cannabis withdrawal when compared to placebo, including effects on withdrawal-related irritability, depression and cannabis cravings. Moreover, the active treatment improved patient retention. Sativex® had a limited, but positive, therapeutic benefit on sleep disturbance, anxiety, appetite loss, physical symptoms and restlessness. The authors did not report significant differences in adverse effects in the groups.

A second RCT assessed the feasibility/effects of fixed (hourly spray) and self-titrated dosages (up to five sprays every hour) of Sativex® on craving and cannabis withdrawal symptoms among nine community-recruited cannabis-dependent subjects, treated during 8 weeks. Patients treated with Sativex® reported fewer withdrawal symptoms in comparison to the corresponding placebo. No significant changes were observed in craving scores between Sativex® and placebo treatment. No serious AEs were reported in association with the medication (Trigo et al. 2016). The study presented a small sample size, a lack of standardisation of dosing, short duration and was restricted to Caucasian males, thus hindering generalisation of the results.

Considering these results, we may conclude that the category of evidence for the use of Sativex® in the treatment of withdrawal in cannabis-dependent patients is B and recommendation grade 3. The use of oral CBD for the treatment of cannabis dependence has grade C2 and grade 4.

Discussion

We performed an extensive systematic review on the benefits and adverse effects associated with medical use of CBD in the most prevalent psychiatric disorders. This review followed recommendations for rigorous systematic reviews (Hutton et al. 2015) and, to the best of our knowledge, this was the first comprehensive systematic review that assessed and graded in levels of evidence the use of CBD for treatment of the most prevalent psychiatric disorders. Previous studies assessed the use of CBD in general medical conditions (Whiting et al. 2015) or in only one group of psychiatric disorders (Ashton et al. 2005; Prud'homme et al. 2015; Gururajan & Malone 2016), and most of them have not graded the level of evidence. Our conclusions are based on the results reported in six case reports and seven RCTs, comprising 201 subjects included in these studies. We found a significant number of studies assessing CBD in pre-clinical, experimental, expert opinions and reviews. As our main goal was to assess the efficacy and safety of the clinical use of CBD, we have not included, in our analysis, studies performed in non-clinical samples and/or which the primary goal was to test a non-clinical intervention.

Our review analysed trial results assessing the effects of CBD in positive symptoms of TRS and first-episode psychosis, in point reduction of anxiety in SAD, cigarette consumption in tobacco dependence, withdrawal symptoms and cannabis dependence. We have not found studies of CBD use in major depression and only one case report with negative results in bipolar disorder.

Most of the studies found suggested that CBD correlated with improvements in symptoms, but these associations, frequently, did not reach statistical significance or the study presented several major limitations that may hinder generalisation or long-term assessment of their results. Several studies presented underpowered samples, elevated risk of bias in sample selection, subjective measures for the evaluation of primary goals and non-replicable settings for clinical practice. As previously reported in another review evaluating the use of CBD in general clinical conditions, there was low or very low quality of evidence to suggest that CBD may be beneficial for the treatment of psychiatric disorders (Whiting et al. 2015).

Multiple formulations of CBD (e.g. tablets, oral capsules, vaporised, oromucosal spray, powder in oil or THC-associated formulations) with a variable dose range (18–1500 mg) and self-titration strategies were used in the studies resulting in a very heterogeneous set of included studies, hindering inter-study

comparison. Moreover, the great variability in dosing may have influenced the results of the described studies regarding efficacy and AEs. Also, studies using crossover designs permitted unblinding due to AEs or the action of an active comparator.

The majority of the studies here described used pure presentations of CBD or formulations with known concentrations of CBD and THC and, hence, their results cannot be extended to non-purified forms, extracts or smoked cannabis. Impure formulations of CBD should be regarded with care for the treatment of psychiatric disorders. The FDA warned in 2015 that one-third of the assessed over-the-counter CBD preparations did not contain CBD (U.S. Food & Drug Administration 2015).

As may be seen in Table 3, we have graded the level of evidence and recommendation grades according to the strategy used by Bandelow et al. (2008). However, our results should be carefully regarded considering the major study limitations described above. Besides cannabis withdrawal, which presented an evidence level of B (e.g., limited positive evidence from RCTs, based on one or more RCTs showing superiority to placebo), CBD use for the treatment of other disorders were graded C or lower. The treatment of positive symptoms of schizophrenia and anxiety in SAD was evaluated as level C1 (e.g., evidence from uncontrolled studies) and cannabis dependence was graded C2 (e.g., case reports; evidence is based on one or more positive case reports and no existing negative controlled studies). Finally, the use of CBD for treatment of major depressive disorders and bipolar disorder was rated F (lack of evidence).

AEs were not always carefully detailed in the studies; when reported, they were insignificant or less intense than the comparative treatment. Most of the studies assessed did not report the evaluation of hepatic and renal function nor modifications in metabolic parameters and interactions of CBD with other medications. CBD is a potent inhibitor of hepatic metabolism and may inhibit the metabolism of other drugs, interfering with their levels (Bornheim et al. 1994). The scarcity of information regarding these parameters may limit the assessment of the safety for use of CBD in psychiatric disorders. Bergamaschi et al. (2011), in a systematic review of the safety and side effects of CBD, concluded that CBD is well tolerated and safe in humans at high doses and in the long term. However, CBD AEs and interactions should be carefully monitored in future trials because in vitro and in vivo studies point to potential drug metabolism interactions, cytotoxicity and modifications in receptor activity (Bergamaschi et al. 2011).

For this review, we have identified as many relevant studies as possible employing an extensive range of bibliographic sources including electronic databases, guidelines, systematic reviews as well as searches of the references of the articles assessed. To minimise bias and errors the articles were examined by two independent specialists and misunderstandings were resolved by consensus.

Conclusion

CBD is still a promising treatment for psychiatric disorders (Leweke & Koethe 2008). However, the evidence regarding efficacy and safety of CBD in psychiatry is still scarce. Further larger, well-designed and methodologically sound RCTs are required to confirm the effects of CBD and cannabinoids in psychiatric disorders. Future trials should assess patient-relevant outcomes using standardised measures (Whiting et al. 2015), use Good Clinical Practice (GCP) guidelines for pharmaceutical product trials ([WHO] 2002) as well as report the results using the Consolidated Standards of Reporting Trials - CONSORT (Boers 2010) reporting standards.

Acknowledgements

This study was made possible by the International Network of Research of Restricted or Prohibited Substances by Government Agencies.

Disclosure statement

F.D.G received CME grants, received paid speakership from Janssen and Pfizer; received research grants from Fundação de Amparo à Pesquisa do Estado de Minas Gerais, Brazil) and National Council for Scientific and Technological Development, Cap (Conselho Nacional de Desenvolvimento Tecnológico, Brazil).

The other authors have no conflicts to declare.

Funding

This study was partially supported by FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais, Brazil) under grant APQ-01714-13 and National Council for Scientific and Technological Development, CNPq (Conselho Nacional de Desenvolvimento Tecnológico, Brazil) under grant 486221/2013-0. The funders did not interfere with any procedure regarding the production of this paper. Q7

ORCID

Julia Machado Khoury http://orcid.org/0000-0001-8842-4972

Maila de Castro Lourenço das Neves http://orcid.org/0000-0003-4125-3736
Marco Antônio Valente Roque http://orcid.org/0000-0003-2282-5647
Daniela Alves de Brito Queiroz http://orcid.org/0000-0003-3671-397X
André Augusto Corrêa de Freitas http://orcid.org/0000-0001-9907-3645
Ângelo de Fátima http://orcid.org/0000-0003-2344-5590
Fabrício Moreira http://orcid.org/0000-0002-0824-7302
Frederico Duarte Garcia http://orcid.org/0000-0003-1926-9053

References

Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, Rivas GR, Holland RM, Muhleisen P, Norberg MM, et al. 2014. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiatry. 71:281–291.

Ashton CH, Moore PB. 2011. Endocannabinoid system dysfunction in mood and related disorders. Acta Psychiatr Scand. 124:250–261.

Ashton CH, Moore PB, Gallagher P, Young AH. 2005. Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. J Psychopharmacol. 19:293–300.

Bae JS, Kim JY, Park BL, Kim JH, Kim B, Park CS, Kim BJ, Lee CS, Lee M, Choi WH, et al. 2014. Genetic association analysis of CNR1 and CNR2 polymorphisms with schizophrenia in a Korean population. Psychiatr Genet. 24:225–229.

Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Wfsbp Task Force on Treatment Guidelines for Anxiety O-C, Post-Traumatic Stress D, Zohar J, Hollander E, Kasper S, et al. 2008. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J Biol Psychiatry.9:248–312.

Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schroder N, Nardi AE, et al. 2011. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology. 36:1219–1226.

Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. 2011. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 6:237–249.

Bhattacharyya S, Crippa JA, Martin-Santos R, Winton-Brown T, Fusar-Poli P. 2009. Imaging the neural effects of cannabinoids: current status and future opportunities for psychopharmacology. Curr Pharm Des. 15:2603–2614.

Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, C M, O C, Seal M, Allen P, et al. 2010. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 35:764–774.

Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, Moriello AS, Davis JB, Mechoulam R, Di Marzo V. 2001. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 134:845–852.

Bitencourt RM, Pamplona FA, Takahashi RN. 2008. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur Neuropsychopharmacol. 18:849–859.

Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. 2015. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics. 12:825–836.

Boers M. 2010. Updated Consolidated Standards of Reporting Trials (CONSORT): it just gets better. J Clin Epidemiol. 63:813–814.

Bornheim LM, Everhart ET, Li J, Correia MA. 1994. Induction and genetic regulation of mouse hepatic cytochrome P450 by cannabidiol. Biochem Pharmacol. 48:161–171.

Breuer A, Haj CG, Fogaca MV, Gomes FV, Silva NR, Pedrazzi JF, Del Bel EA, Hallak JC, Crippa JA, Zuardi AW, et al. 2016. Fluorinated cannabidiol derivatives: enhancement of activity in mice models predictive of anxiolytic, antidepressant and antipsychotic effects. PloS One. 11:e0158779.

Campos AC, Ferreira FR, Guimaraes FS. 2012. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. J Psychiatr Res. 46:1501–1510.

Campos AC, Fogaca MV, Sonego AB, Guimaraes FS. 2016. Cannabidiol, neuroprotection and neuropsychiatric disorders. Pharmacol Res. Q1

Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FS. 2012. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Philos Trans R Soc Lond B Biol Sci. 367:3364–3378.

Conselho Federal de Medicina. 2014. RESOLUÇÃO CFM N° 2.113/2014 - Aprova o uso compassivo do canabidiol para o tratamento de epilepsias da criança e do adolescente refratárias aos tratamentos convencionais. In: Brasília.

Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, Simoes MV, Bhattacharyya S, Fusar-Poli P, Atakan Z, et al. 2011. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol. 25:121–130.

Crippa JA, Hallak JE, Machado-de-Sousa JP, Queiroz RH, Bergamaschi M, Chagas MH, Zuardi AW. 2013. Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. J Clin Pharm Ther. 38:162–164.

Crippa JA, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JE, McGuire PK, Filho Busatto G. 2004. Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology. 29:417–426.

Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, Miller I, Flamini R, Wilfong A, Filloux F, et al. 2016. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 15:270–278.

Di Marzo V, Piscitelli F. 2015. The endocannabinoid system and its modulation by phytocannabinoids. Neurotherapeutics. 12:692–698.

Eggan SM, Hashimoto T, Lewis DA. 2008. Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. Arch Gen Psychiatry. 65: 772–784.

Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, Stone JM, Reichenberg A, Brenneisen R, Holt D, et al. 2013. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 27:19–27.

Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, et al. 2009. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry. 66:95–105.

Gardner EL. 2005. Endocannabinoid signaling system and brain reward: emphasis on dopamine. Pharmacol Biochem Behav. 81:263–284.

Gomes FV, Casarotto PC, Resstel LB, Guimaraes FS. 2011. Facilitation of CB1 receptor-mediated neurotransmission decreases marble burying behavior in mice. Prog Neuropsychopharmacol Biol Psychiatry. 35:434–438.

Gomes FV, Issy AC, Ferreira FR, Viveros MP, Del Bel EA, Guimaraes FS. 2014. Cannabidiol attenuates sensorimotor gating disruption and molecular changes induced by chronic antagonism of NMDA receptors in mice. Int J Neuropsychopharmacol. 18.

Q2

Gomes FV, Resstel LB, Guimaraes FS. 2011. The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. Psychopharmacology (Berl). 213:465–473.

Guimaraes VM, Zuardi AW, Del Bel EA, Guimaraes FS. 2004. Cannabidiol increases Fos expression in the nucleus accumbens but not in the dorsal striatum. Life Sci. 75:633–638.

Gururajan A, Malone DT. 2016. Does cannabidiol have a role in the treatment of schizophrenia? ~~Schizophr Res.~~

Q3

GW Pharmaceuticals announces positive phase 3 pivotal study for Epidolex (cannabidiol). 2016. London. Available from: http://www.gwpharm.com/GWPharmaceuticalsAnnouncesPositivPhase3PivotalStudyResultsforEpidiolexcannabidiol.aspx .

Hallak JE, Dursun SM, Bosi DC, de Macedo LR, Machado-de-Sousa JP, Abrao J, Crippa JA, McGuire P, Krystal JH, Baker GB, et al. 2011. The interplay of cannabinoid and NMDA glutamate receptor systems in humans: preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects. Prog Neuropsychopharmacol Biol Psychiatry. 35:198–202.

Heifets BD, Castillo PE. 2009. Endocannabinoid signaling and long-term synaptic plasticity. Annu Rev Physiol. 71:283–306.

Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, et al. 2015. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Int Med. 162:777–784.

Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. 1974. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. Eur J Pharmacol. 28:172–177.

Khoury JM, Roque MAV, Queiroz DAB, Moreira FA, Garcia FD. 2016. Canabidiol em psiquiatria. In: PROPSIQ Programa de Atualização em Psiquiatria: Ciclo 5 Porto Alegre: Artmed Panamericana. p. 9–63.

Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. 2015. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 172:4790–4805.

Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D. 1999. Elevated endogenous cannabinoids in schizophrenia. Neuroreport. 10:1665–1669.

Leweke FM, Koethe D. 2008. Cannabis and psychiatric disorders: it is not only addiction. Addict Biol. 13:264–275.

Leweke FM, Mueller JK, Lange B, Rohleder C. 2016. Therapeutic Potential of Cannabinoids in Psychosis. Biol Psychiatry. 79:604–612.

Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkotter J, Hellmich M, Koethe D. 2012. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2:e94.

Leweke M. 2013. The endocannabinoid system in schizophrenia - a mechanistically new approach to its pathophysiology and treatment. ~~Schizophr Bull. 39 (Suppl 1):S341.~~

Ligresti A, De Petrocellis L, Di Marzo V. 2016. From phytocannabinoids to cannabinoid receptors and endocannabinoids: pleiotropic physiological and pathological roles through complex pharmacology. Physiol Rev. 96: 1593–1659.

Linge R, Jimenez-Sanchez L, Campa L, Pilar-Cuellar F, Vidal R, Pazos A, Adell A, Diaz A. 2016. Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. Neuropharmacology. 103:16–26.

Lu HC, Mackie K. 2016. An introduction to the endogenous cannabinoid system. Biol Psychiatry. 79:516–525.

Mechoulam R, Gaoni Y, Hashish IV. 1965. The isolation and structure of cannabinolic cannabidiolic and cannabigerolic acids. Tetrahedron. 21:1223–1229.

Meltzer HY, Arvanitis L, Bauer D, Rein W. Meta-Trial Study G. 2004. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. Am J Psychiatry. 161:975–984.

Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. 2013. Endocannabinoid system and mood disorders: priming a target for new therapies. Pharmacol Ther. 138:18–37.

Moreira FA, Guimaraes FS. 2005. Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. Eur J Pharmacol. 512:199–205.

Morgan CJ, Curran HV. 2008. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry. 192:306–307.

Morgan CJ, Das RK, Joye A, Curran HV, Kamboj SK. 2013. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. Addict Behav. 38: 2433–2436.

Morgan CJ, Gardener C, Schafer G, Swan S, Demarchi C, Freeman TP, Warrington P, Rupasinghe I, Ramoutar A, Tan N, et al. 2012. Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychol Med. 42:391–400.

Pedrazzi JF, Issy AC, Gomes FV, Guimaraes FS, Del-Bel EA. 2015. Cannabidiol effects in the prepulse inhibition

disruption induced by amphetamine. Psychopharmacology (Berl). 232:3057–3065.
Pertwee RG. 2005. Pharmacological actions of cannabinoids. In: Cannabinoids. Heidelberg: Springer Berlin. p. 1–51.
Pertwee RG, Ross RA, Craib SJ, Thomas A. 2002. (-)-Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens. Eur J Pharmacol. 456:99–106.
Prud'homme M, Cata R, Jutras-Aswad D. 2015. Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence. Substance abuse: research and treatment. 9:33–38.
Russo EB, Burnett A, Hall B, Parker KK. 2005. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 30:1037–1043.
Sagheddu C, Muntoni AL, Pistis M, Melis M. 2015. Endocannabinoid signaling in motivation, reward, and addiction: influences on mesocorticolimbic dopamine function. IntRev Neurobiol. 125:257–302.
Sartim AG, Guimaraes FS, Joca SR. 2016. Antidepressant-like effect of cannabidiol injection into the ventral medial prefrontal cortex-Possible involvement of 5-HT1A and CB1 receptors. Behav Brain Res. 303:218–227.
Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP. 2011. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr Res. 130:216–221.
Shannon S, Opila-Lehman J. 2015. Cannabidiol oil for decreasing addictive use of marijuana: a case report. Integr Med (Encinitas). 14:31–35.
Trigo JM, Lagzdins D, Rehm J, Selby P, Gamaleddin I, Fischer B, Barnes AJ, Huestis MA, Le Foll B. 2016. Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. Drug Alcohol Depend. 161:298–306.
Trigo JM, Soliman A, Staios G, Quilty L, Fischer B, George TP, Rehm J, Selby P, Barnes AJ, Huestis MA, et al. 2016. Sativex associated with behavioral-relapse prevention strategy as treatment for cannabis dependence. A case series. J Addict Med. 10:274–279.
Warning letters and test results for cannabidiol-related products. 2015. Available from http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm
WHO. 2002. Handbook for clinical research practice (GCP). In: Geneva: Office of Publications, World Health Organization.
Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, et al. 2015. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 313:2456–2473.
Winton-Brown TT, Allen P, Bhattacharyya S, Borgwardt SJ, Fusar-Poli P, Crippa JA, Seal ML, Martin-Santos R, Ffytche D, Zuardi AW, et al. 2011. Modulation of auditory and visual processing by delta-9-tetrahydrocannabinol and cannabidiol: an FMRI study. Neuropsychopharmacology. 36:1340–1348.
Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SR. 2010. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. Br J Pharmacol. 159:122–128.
Zuardi A, Crippa J, Dursun S, Morais S, Vilela J, Sanches R, Hallak J. 2010. Cannabidiol was ineffective for manic episode of bipolar affective disorder. J Psychopharmacol. 24:135–137.
Zuardi AW, Cosme RA, Graeff FG, Guimaraes FS. 1993. Effects of ipsapirone and cannabidiol on human experimental anxiety. J Psychopharmacol (Oxford). 7:82–88.
Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE, Crippa JA. 2006. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol (Oxford) 20:683–686.
Zuardi AW, Morais SL, Guimaraes FS, Mechoulam R. 1995. Antipsychotic effect of cannabidiol. J Clin Psychiatry. 56:485–486.
Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. 1982. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology (Berl). 76:245–250.