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Cannabidiol (CBD) Use in Psychiatric Disorders; A Systematic Review

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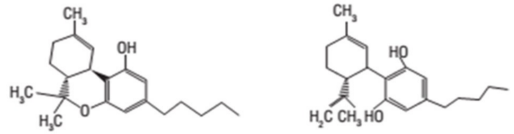
Abstract

Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) are the most represented phytocannabinoids in Cannabis sativa plants. However, CBD may present with a different activity compared with the psychotomimetic THC. Most typically, CBD is reported to be used in some medical conditions, including chronic pain. Conversely, the main aim of this systematic review is to assess and summarise the available body of evidence relating to both efficacy and safety of CBD as a treatment for psychiatric disorders, alone and/or in combination with other treatments. Eligible studies included randomized controlled trials (RCT) assessing the effect of CBD in a range of psychopathological conditions, such as substance use; psychosis, anxiety, mood disturbances, and other psychiatric (e.g., cognitive impairment; sleep; personality; eating; obsessive-compulsive; post-traumatic stress/PTSD; dissociative; and somatic) disorders. For data gathering purposes, the PRISMA guidelines were followed. The initial search strategy identified some n=1,301 papers; n=190 studies were included after the abstract's screening and n=27 articles met the inclusion criteria. There is currently limited evidence regarding the safety and efficacy of CBD for the treatment of psychiatric disorders. However, available trials reported potential therapeutic effects for specific psychopathological conditions, such as substance use disorders, chronic psychosis, and anxiety. Further large-scale RCTs are required to better evaluate the efficacy of CBD in both acute and chronic illnesses, special categories, as well as to exclude any possible abuse liability.

Background

Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) are the most represented phytocannabinoids in Cannabis sativa plants (Crippa et al., 2018; Corroon and Phillips, 2018; Ligresti et al., 2016). CBD was isolated from cannabis extracts in the 1940s (Adams et al., 1940) and, even though initially considered a non-active cannabinoid (Crippa et al., 2018; Zuardi, 2008), it was then recognised as presenting with a different activity compared with the psychotomimetic THC (Casajuana Köguel et al., 2018; Crippa et al., 2018; Ligresti et al., 2016; Mechoulam et al., 1970; Zuardi et al., 1982), due to a combination of pharmacokinetic and pharmacodynamic interactions (Crippa et al., 2018; Lafaye et al., 2017; Ligresti et al., 2016; Zuardi et al., 1982). For istance, the exogenous cannabinoid CBD acts on the neuromodulatory endocannabinoid system (eCBS), which plays important roles in central nervous system (CNS) development, synaptic plasticity, and response to endogenous and environmental insults (Lu and Mackie, 2016). The endogenous eCBS' ligands, e.g. anandamide/N-arachidonoylethanolamine (AEA) and 2-arachidonoyl-sn-glycerol (2-AG), act as agonists of the metabotropic CB1/CB2 receptors. Conversely, CBD displays a very low affinity for these two receptors (Devane et al., 1992), whilst exerting an antagonist or negative modulatory action (Ligresti et al., 2016). CBD can also facilitate eCBS' signalling and influence endocannabinoid levels, whilst inhibiting their cellular re-uptake by binding to fatty acid binding proteins (FABPs) (Elmes et al., 2015). Moreover, CBD decreases the endocannabinoids' hydrolysis mediated by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (Ligresti et al., 2016; Campos et al., 2012). CBD can also promote the blockade of adenosine uptake and act as an agonist of both the transient receptor potential vanilloid ion channel TRPV1 and the serotonergic 5-HT1A receptors (Bisogno et al., 2001; Boggs et al., 2018a; Campos et al., 2017; Campos and Guimarães, 2008; Thomas et al., 2007). Finally, CBD reportedly presents with a better safety profile compared to other CBs, such as THC; in fact, even at high dose of 1,500 mg a day CBD seems to be well tolerated both in animals and humans (Boggs et al., 2018a; Campos et al., 2017). Both THC and CBD are substrates and inhibitors of cytochrome P450 enzymatic pathways relevant to the biotransformation of commonly prescribed psychotropic agents, hence further studies are needed to assess the potential drug-drug-interactions (DDIs) (Rong et al., 2017).



Δ9-THC Cannabidiol

Chemical structures of Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD)

Regarding the medicinal cannabis use, the oldest description encrypted on an Egyptian stone dates back to around 2350 B.C. (Ligresti et al., 2016). Currently, CBD is generally considered a cannabinoid compound with both a wide range of pharmacological effects and a broad spectrum of potential clinical use (Campos et al., 2017; Crippa et al., 2018; Pisanti et al., 2017; Zuardi, 2008). The worldwide regulatory status of CBD is complex and constantly changing, but CBD can currently be purchased online; over the counter; and from cannabis-specific dispensaries in some countries like the US (Corroon and Phillips, 2018; Ware and Tawfik, 2005). As a result, according to a large-scale survey recently conducted on 2,409 internet buyers, CBD has been reported to be used in almost 4,000 medical conditions; typically including: chronic pain, arthritis/joint pain, anxiety, depression, and sleep disorders (Corroon and Phillips, 2018). Although CBD may present with anti-oxidant, anti-inflammatory, neuroprotective, anti-convulsant, anti-emetic and analgesic effects, it has been proven to be effective only in a narrow range of medical conditions, such as: epilepsy; chronic pain; and intractable chemotherapy-induced nausea and vomiting (Campos et al., 2016; Mandolini et al., 2018; Mannucci et al., 2017; Noel, 2018; Pisanti et al., 2017; Scuderi et al., 2009). In psychiatry, CBD has been suggested to possess antipsychotic, antidepressant, anxiolytic, anti-craving and pro-cognitive activities (Bhattacharyya et al., 2010; Hill et al., 2012; Mandolini et al., 2018; National Academies of Sciences, Engineering, and Medicine, 2017; Noel, 2018; Parolaro et al., 2010; Pisanti et al., 2017; Scherma et al., 2018; Crippa et al., 2018; Jurkus et al., 2016). However, reliable information is still needed, and the main aim of this systematic review was to assess and summarise the available body of evidence relating to both efficacy and safety of CBD use in patients with psychiatric disorders.

Materials and Methods

Search strategy

A systematic electronic search was performed on 31st January 2019 on a range of international databases, including PubMed, Cochrane Controlled Register of Trials (CENTRAL), and Web of Science. The systematic review was structured in accordance with the PRISMA guidelines (Moher et al., 2009). The search terms “cannabidiol” and “CBD” were combined with “substance use disorders”, “psychotic disorders”, “anxiety disorders”, “mood disorders”, “cognitive disorders”, “sleep disorders”, “personality disorders”, “eating disorders”, “obsessive compulsive disorders”, “trauma stress disorders”, “dissociative disorders”, and “somatic disorders”. Identified studies were assessed at title/abstract and full text screening against eligibility criteria. The reference lists of included studies were also manually searched to identify additional citations (Table 1).

Cannabidiol AND (+ key words listed below)	Total n of records finding through searching database up to January 2019.			Total n of records included after abstract screening.			Total n of papers included after full-text screening.			Total n of RCT included after backward search.
	PM	C	WS	PM	C	WS	PM	C	WS	Number
1. Substance use disorders	133	18	8	31	5	2	4	5	2	**6**
2. Psychotic disorders	68	35	23	39	14	6	4	15	6	**9**
3. Anxiety disorders	71	22	8	23	8	3	2	4	3	**3**
4. Mood disorders	20	21	1	7	2	0	0	2	0	**1**

5. Other psychiatric disorders:										
a. Neurocognitive	469	50	21	24	4	0	1	4	0	**4**
b. Sleep	52	25	3	13	0	1	0	0	0	**0**
c. Personality	19	10	0	1	2	0	1	2	0	**1**
d. Eating	39	3	0	0	0	0	0	0	0	**0**
e. Obsessive-Compulsive	6	1	0	0	1	0	0	0	0	**0**
f. Trauma Stress	141	14	2	0	3	0	0	0	0	**3**
g. Dissociative	13	2	1	1	0	0	0	0	0	**0**
h. Somatic	2	0	0	0	0	0	0	0	0	**0**

Table 1: Results from a systematic literature search, updated in January 2019, relating to the role of CBD in a range of psychopathological conditions conducted by using the online PubMed (PM), CENTRAL (C) and Web of Science (WS) databases.

Inclusion/exclusion criteria

To evaluate efficacy and safety of CBD-based interventions, only Randomised Controlled Trials (RCTs) that recruited patients presenting with substance use disorders, psychosis, anxiety, mood and other psychiatric disorders were here considered. To provide the reader with the most updated information, details of ongoing RCTs were included as well.

Data synthesis strategy

Data were extracted by n=3 reviewers (AR, CZ, SC), while n=2 senior researchers (SB, FS) supervised all stages of the process and were consulted to resolve any possible disagreement. Data on intervention and its administration, duration, sample characteristics and outcomes were extracted (Table 2).

TRIAL	AIMS	STUDY DESIGN	DURATION	SAMPLE	DRUG	OUTCOME
SUBSTANCE USE DISORDERS						
Allsop et al., 2014	Safety and efficacy of nabiximols in treating cannabis withdrawal.	Drug versus placebo double-blind RCT.	6 days of treatment/placebo + 3 days of wash-out + 28 days of follow-up.	51 inpatients with cannabis dependence according to DSM-IV with no current alcohol or other drug dependence except for nicotine and/or caffeine; experienced withdrawal during previous quit attempts; desired to reduce or quit cannabis use.	Nabiximols oro-mucosal spray, maximum daily dose: 86.4 mg of Δ9-tetrahydrocannabinol and 80 mg of cannabidiol.	Reduction in the overall severity of cannabis withdrawal relative to placebo, including effects on withdrawal-related irritability, depression, and cannabis cravings. More limited benefit on sleep disturbance, anxiety, appetite loss, physical symptoms, and restlessness. Number and severity of adverse events not significantly different between groups.
Bhardwaj et al., 2018	Efficacy, safety and cost-effectiveness of longer-term nabiximols treatment in resistant to treatment outpatients with cannabis dependence.	Drug versus placebo, phase III multi-site double-blind, parallel RCT.	12 weeks of treatment/placebo + 24 weeks of follow-up.	142 outpatients with cannabis dependence according to ICD-10 criteria; with inability to stop cannabis use in previous attempts, operationalised as relapse to cannabis use within one month of a substantive cessation attempt.	Nabiximols oromucosal spray, maximum daily dose: 32 sprays; 8 sprays (total 21.6 mg THC and 20 mg CBD) four times a day.	Ongoing.
Hindocha et al., 2018	Effect of CBD on attentional bias, pleasantness of cigarette-related stimuli, craving and withdrawal symptoms and its tolerability.	Drug versus placebo, double-blind crossover RCT.	One acute administration.	30 non-treatment seeking individuals with smoking dependence.	800 mg CBD orally.	Placebo, but not CBD group, was associated with increased attentional bias during abstinence. CBD also reduced explicit pleasantness of cigarette images. CBD did not influence withdrawal nor craving.
Hurd et al., 2015	Efficacy of CBD in heroin	Drug versus Drug versus	3 sessions each preceded by	Opioid-dependent	First group: 400 mg CBD	A single administration of

	craving.	placebo, double-blind RCT.	one acute administration of treatment/placebo + follow up 7 days after the study end.	individuals with no dependence on any other drug than heroin according to DSM-IV; abstinent for at least 7 days.	orally. Second group: 800 mg CBD orally.	CBD, in comparison to placebo, attenuated subjective cue-induced craving measured after 1 h, maintained a decrease of general craving 24 h later, and persisted even 7 days after the last treatment.
Trigo et al., 2015	Effects of Sativex® on craving and withdrawal in community cannabis-dependent individuals.	Drug versus placebo, double-blind, 8-condition (ABACADAE design) RCT.	4 smoke as usual conditions (A) separated by 4 cannabis abstinence conditions (B–E), with administration of either self-titrated/fixed doses of placebo or Sativex®.	9 individuals with cannabis-dependence; not seeking treatment for cannabis dependence.	Self-titration of Sativex®: up to a maximum of 40 sprays (equal to 108 mg THC). Fixed dose of Sativex®: 40 sprays.	Decrease withdrawal scores during the fixed and self-titrated dose conditions. None of the placebo conditions reduced withdrawal. No changes in craving were observed in this study. No severe adverse effects were associated with the study medication.
Trigo et al., 2018	Tolerability and safety of self-titrated nabiximols concurrently with MET/CBT among treatment-seeking cannabis-dependent participants.	Drug versus placebo, double-blind RCT.	12 weeks of treatment/placebo and MET/CBT once a week.	40 individuals met DSM-IV criteria for current cannabis dependence; treatment-seeking for cannabis dependence.	Self-titration of nabiximols, up to a maximum of 42 sprays (equal to 113.4 mg THC/105 mg CBD daily).	No serious adverse events observed; no difference in rates of adverse events between groups. No significant change in abstinence rates at trial end; cannabis use reduced in both groups. Nabiximols reduced cannabis craving but no significant differences between groups were observed on withdrawal scores.
PSYCHOTIC DISORDERS						
Bhattacharayya et al., 2016	Anti-psychotic properties of an acute dose of CBD in ultra-high-risk individuals, studied by virtual reality.	Drug versus placebo RCT.	7 days of treatment/placebo.	23 ultra-high risk individuals.	600 mg/die CBD oral capsules.	CBD group showed significantly less paranoia and anxiety compared with placebo group, following exposure to the virtual reality environment.
Bhattacharayya et al., 2018	Investigate by fRMI the neurocognitive mechanisms that underlie the therapeutic effects of	Drug versus placebo versus Healthy control parallel-group, double-blind RCT.	One acute administration.	33 antipsychotic medication–naïve participants at clinical high risk of psychosis + 19	600 mg CBD oral capsules.	CBD group presented an activation of right caudate during encoding and in the parahippocampal gyrus and

	CBD in psychosis.			healthy controls.		midbrain during recall that was greater than in the placebo group but lower than in the control group.
Boggs et al., 2018b	Cognitive, symptomatic, and side effects of CBD versus placebo in patients with schizophrenia.	Drug versus placebo double-blind RTC.	6 weeks of treatment/placebo.	Outpatients with chronic schizophrenia or schizoaffective disorder, according to DSM-IV and confirmed by SCID.	600 mg/die CBD oral capsules.	CBD failed to prove any cognitive improvement, measured by MATRICS Consensus Cognitive Battery, compared with placebo. PANSS total scores decreased over time, but there was no significant drug × time interaction. Side effects were similar between CBD and placebo, with the one exception being sedation.
Leweke et al., 2010	Efficacy of CBD in first-break schizophrenia patients.	Drug versus placebo double-blind, cross-over RCT.	14 days of treatment/placebo + 14 days of the opposite condition.	29 antipsychotic-naive, first-break paranoid schizophrenia patients, fulfilling diagnostic criteria of DSM-IV.	600 mg/die CBD orally.	CBD significantly improved psychotic symptoms in the CBD-placebo condition during the first 14 days of treatment when compared to baseline. Only one patient on sequence CBD-placebo terminated treatment early, whereas 10 patients terminated early on sequence placebo-CBD. The most frequent reason given was worsening of symptoms.
Leweke et al., 2012a	Efficacy and tolerability of CBD in patients with schizophrenia.	Drug versus Drug double-blind, parallel-group, RCT.	4 weeks of treatment/placebo.	42 inpatients with schizophrenia; BPRS>36; BPRS-THOT>12.	First group: up to 800 mg/die CBD orally. Second group: up to 800 mg/die amisulpride orally.	Both groups showed significant clinical improvement. CBD displayed a superior side-effect profile. CBD treatment was accompanied by a significant increase in serum anandamide levels, which was significantly associated with clinical improvement.

Leweke et al., 2014a	Efficacy of CBD as add-on of antipsychotic therapy in FEP patients.	Drug versus placebo double-blind RCT.	24 weeks of treatment/placebo + 2 weeks of withdrawal + 24 weeks of follow-up.	180 FEP.	800 mg /die of CBD orally.	Ongoing.
McGuire et al., 2018a	Safety and effectiveness of CBD in patients with schizophrenia.	Drug versus placebo double-blind parallel-group RCT.	6 weeks of treatment/placebo + follow up at day 42 and 57.	88 patients with schizophrenia or a related psychotic disorder according to DSM-IV; stable dosage of antipsychotic medication for at least 4 weeks.	10 mL of a 100 mg/mL CBD oral solution.	Lower levels of positive psychotic symptoms at PANSS score, higher improved at CGI-I and CGI-S found in CBD group. CBD also showed greater improvements in cognitive performance and in overall functioning. Rates of adverse events were similar between the CBD and placebo groups.
O'Neill et al., 2018	Effects of CBD on the neural substrates implicated in memory and learning in FEP subjects.	Drug versus placebo double-blind, repeated measures, within subject cross over RCT.	2 sessions each preceded by one acute administration (1 with treatment/placebo and 1 with the opposite condition) + at least 1 week of wash-out between sessions.	17 patients with FEP.	600 mg CBD oral capsules.	Decrease in activity in the left hippocampus and the right parahippocampal gyrus during the recall condition, within the FEP group. No significant differences between placebo and CBD functional activity were observed during the encoding condition. No significant differences were observed between FEP participant performances on the CBD and placebo study days.
Ranganathan et al., 2018	Effects and tolerability of CBD in early course patients with schizophrenia.	Drug versus placebo double-blind cross-over RCT.	4 weeks of treatment/placebo +2 weeks washout + 4 weeks of opposite condition.	72 patients with schizophrenia within the first 7 years of their psychotic illness.	800 mg/die CBD orally.	Ongoing.
ANXIETY DISORDERS						
Bergamaschi et al., 2011	Effects of a single dose of CBD in patients with SAD during a simulation public speaking test.	Drug versus placebo versus healthy control double-blind RCT.	One acute administration.	24 volunteers with SAD according to SCID + 12 healthy controls.	600 mg CBD oral capsules.	Pre-treatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and

						significantly decreased alert in their anticipatory speech, compared with placebo. No differences found between CBD group and healthy controls.
Crippa et al., 2011	Neural and behavioural effects of CBD in patients with SAD, evaluating by (99m)Tc-ECD SPECT.	Drug versus placebo double-blind cross-over RCT.	2 sessions each preceded by one acute administration of treatment/placebo.	10 right-handed treatment-naïve men with SAD confirmed by the SCID for the DSM-IV.	400 mg CBD orally.	Significant decrease in subjective anxiety after CBD. Reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus and increased ECD uptake in the right posterior cingulate gyrus after CBD.
NCT03549819	Efficacy of daily CBD in treating symptoms of DSM-5 anxiety disorders.	Drug versus placebo, double-blind RCT.	8 weeks of treatment placebo + 2 weeks follow-up.	50 patients with a primary psychiatric diagnosis of either GAD, SAD, PD or agoraphobia as defined by DSM-5 criteria and a HAM-A score of ≥ 22	Up to 800mg/die CBD oral capsules.	Ongoing.
MOOD DISORDERS						
NCT03310593	Effects of CBD on depressive and anxiety symptoms, functioning and inflammatory biomarkers.	Drug versus placebo, double-blind RCT.	12 weeks of treatment/placebo.	100 patients with major depressive episode as part of bipolar I or II disorder according to DSM-5.	600 mg/die CBD oral.	Ongoing.
NEUROCOGNITIVE DISORDERS						
Chagas et al., 2013	Efficacy and safety of CBD added to treatment as usual in patients with Parkinson and its effects in relation to concentrations of brain metabolites (N-acetyl-aspartate, creatine and choline) in the basal ganglia.	Drug versus Drug versus placebo double-blind RCT.	6 weeks of treatment/placebo.	20 patients with a confirmed diagnosis of idiopathic Parkinson Disease without dementia and on stable doses of anti-Parkinson drugs for at least 30 days.	First group: 75 mg CBD orally. Second group: 300 mg CBD orally.	CBD 300 mg had a significantly greater decrease in PDQ-39 scores from baseline than the other 2 groups. No changes of brain metabolites were observed in any group. No adverse effects were observed with the introduction of CBD.
Consroe et al., 1991	Efficacy and safety of CBD in drug-näive patients with Huntington disease.	Drug versus placebo double-blind cross-over RCT.	6 weeks of treatment/placebo.	15 patients with Huntington's Disease, neuroleptic-free for at least 2 weeks before the trial start and till the end of it.	10 mg/kg/day CBD orally.	No significant differences in neither effect on symptoms, laboratory analyses nor side effects between CBD and placebo

						groups.
Lopez- Sendon Moreno et al., 2016	Safety and efficacy of CBD in patients with Huntington disease.	Drug versus placebo double-blind, cross-over RCT.	12 weeks of treatment/placebo + 4 weeks of wash-out + 12 weeks of the opposite substance.	26 patients with HD with stable baseline medication for at least 6 weeks prior to randomization.	12 spray/die Sativex® oral spray.	No significant molecular or symptomatic effects was detected.
NCT03639064	Tolerability, safety and dose-finding of oil cannabis preparation for pain in Parkinson's disease.	Drug versus Drug versus Drug, double-blind RCT.	35 days of treatment/placebo.	15 patients with Parkinson disease.	First group: cannabis oil with concentration of THC/CBD 18/0. Second group: cannabis oil with concentration of 10/10. Third group: cannabis oil with concentration of 1/20.	Ongoing.
PERSONALITY DISORDERS						
Hindocha et al., 2015,	Effects of THC and CBD, both alone and in combination on psychotic symptoms and memory function.	Drug versus Drug versus Drug versus placebo double-blind, cross-over RCT.	4 administration (1 for each compound), each separated by a one-week wash-out.	48 cannabis users from the community divided on the basis of (1) schizotypal personality questionnaire scores (low, high) and (2) frequency of cannabis use (light, heavy).	First group: 8 mg THC inhaled through a vaporiser Second group: 8 mg THC + 16 mg CBD inhaled through a vaporiser Third group: 16 mg CBD inhaled through a vaporiser.	Improvement in facial emotion recognition after CBD administration for both high and low schizotypy groups.
Morgan et al., 2018	Effects of THC and CBD, both alone and in combination on psychotic symptoms and memory function.	Drug versus Drug versus Drug versus placebo double-blind, cross-over RCT.	4 administration (1 for each compound), each separated by a one-week wash-out.	48 cannabis users from the community divided on the basis of (1) schizotypal personality questionnaire scores (low, high) and (2) frequency of cannabis use (light, heavy).	First group: 8 mg THC inhaled through a vaporiser Second group: 8 mg THC + 16 mg CBD inhaled through a vaporiser Third group: 16 mg CBD inhaled through a vaporiser.	THC increased overall scores on the PSI, negative symptoms on BPRS, and impaired episodic and working memory. Co-administration of CBD failed to attenuate these effects. CBD alone reduced PSI scores in light users only. No difference found between low and high schizotypy.
TRAUMA AND STRESS-RELATED DISORDERS						
NCT02759185	Effects of cannabis on PTSD symptoms.	Drug versus Drug versus Drug versus placebo, double-blind RCT.	3 weeks of treatment/placebo + 2 weeks of abstinence + 3 weeks of another condition.	76 veterans with chronic (at least six months' duration) PTSD.	First group: High THC Marijuana (THC > CBD) Second group: High CBD Marijuana (THC < CBD) Third group: High THC/high CBD marijuana (THC = CBD). Maximum daily dose for each group: 1,8 g of marijuana.	Ongoing.

NCT03248167	Efficacy of CBD in treating alcohol use disorder in individuals with PTSD.	Drug versus placebo, triple-blind, cross-over RCT.	6 weeks of treatment/placebo.	50 patients with moderate/severe AUD according to DSM 5 criteria; PTSD with a Clinician Administered PTSD Scale current symptom score > 25.	400 mg/die CBD orally.	Ongoing.
NCT03518801	Efficacy of CBD and concurrently prolonged exposure therapy in treating PTSD symptoms.	Drug versus placebo, double-blind RCT.	16 weeks of treatment/placebo + 1-month follow-up + 3-month follow-up	136 veterans with PTSD according to DSM-5 criteria.	Not stated.	Ongoing.

Legenda: BPRS: Brief Psychiatric Rating Scale; **BPRS-THOT**: Brief Psychiatric Rating Scale -Thought Disorders item; **CBD**: cannabidiol; **CGI-I**: Clinical Global Impression-Improvement; **CGI-S**: Clinical Global Impression-Severity; **DSM-IV**: Diagnostic and Statistical Manual of mental disorders IV edition; **DSM-5**: Diagnostic and Statistical Manual of mental disorders 5th edition; **ECD**: Ethyl Cysteinate Dimer; **FEP**: first episode psychosis; **fMRI**: functional Magnetic Resonance Imaging; **GAD**: Generalised Anxiety Disorder; **HAM-A**: Hamilton Anxiety Scale; **ICD-10**: International Classification of Diseases, 10th edition; **MATRICS**: Measurement and Treatment Research to Improve Cognition in Schizophrenia; **MET/CBT**: Motivational Enhancement Therapy/Cognitive Behavioural Therapy; **PANSS**: Positive And Negative Schizophrenic Symptoms; **PD**: Panic Disorder; **PDQ-39**: Parkinson's Disease Questionnaire; **PTSD**: Post Traumatic Stress Disorder; **RCT**: Randomised Clinical Trial; **SAD**: Social Anxiety Disorder; **SCID**: Structured Clinical Interview for DSM-5; **THC**: Tetra-hydro-cannabinol; **(99-m)Tc-ECD SPECT**: 99mTc-Ethyl Cysteinate Dimer Single Photon Emission Computed Tomography.

Table 2: Description of the identified RTCs, up to January 2019, focusing on the therapeutic role of CBD in a range of psychopathological conditions. The systematic literature search was conducted by using the PubMed, Cochrane Library and Web of Science databases.

Results

The initial search strategy yielded a total of n=1,301 articles that were screened by title and abstract for eligibility. A total of n=190 studies passed the title/abstract screening and were considered for full-text screening. Of these studies, n=135 were excluded, as either mostly referring to preclinical models, or due to inappropriate study design/population. The remaining n=55 were searched for duplicates, and secondary publications were aggregated in study-based units. Thus, n=27 RCTs were included in this systematic review (Table 1). The results are here presented as follows: 1) CBD and substance use disorders; 2) CBD and psychotic disorders; 3) CBD and anxiety disorders; 4) CBD and mood disorders; and 5) CBD and other psychiatric conditions (cognitive disorders, sleep disorders, personality disorders, eating disorders, obsessive compulsive disorders, trauma stress disorders, dissociative disorders, and somatic disorders).

CBD and substance use disorders

Background

The eCBS appears to be involved in both acquisition and maintenance of drug-seeking behaviour, possibly through its role in reward system and brain plasticity (National Academies of Sciences, Engineering, and Medicine, 2017). The dopaminergic pathway activation, linking the ventral tegmental area; the ventral striatum; and the nucleus accumbens, plays a central role in the reward circuit (Chye et al., 2019). In animal models, the CB1 receptor is identified in striatal output projection neurons of the nucleus accumbens and dorsal striatum (Zhang et al., 2014), while the CB2 receptor seems to be expressed in dopamine neurons of the ventral tegmental area, related to drug reinforcement behaviour (Xi et al., 2011). Moreover, CB1 receptors are also present in the corticostriatal circuit, thus an alteration of eCBS could ultimately lead to a dysregulation of the glutamatergic cortex neurons affecting the neuroplasticity process (Chye et al., 2019). In line with this, pre-clinical and clinical studies have suggested that CBD could interfere with both craving and withdrawal symptoms' development. In fact, CBD may present with anti-addiction properties by reducing expression of drug memories, both acutely and through the disruption of their reconsolidation (Lee et al., 2017; Chye et al., 2019). Two mechanisms, mainly relating to the modulation of the endocannabinoid, serotoninergic and glutamatergic systems, have been hypothesised as a possible explanation of the potential anti-addiction clinical properties of CBD. First, CBD agonist activities on 5-HT1A receptors may contribute to its anti-craving effects, and help reducing relapses by regulating the drug reward system, anxiety symptoms and improving stress management (Prud'Homme et al., 2015). Second, CBD acts as a regulator of the glutamatergic signalling through the modulation of the serotoninergic and the endocannabinoid systems. This may have a role in the treatment of addictive behaviour (Rodríguez-Muñoz et al., 2016), since a dysregulation of glutamatergic transmission has been widely related to both drug-seeking behaviour and relapse occurrence (Prud'Homme et al., 2015).
In rodent models, CBD exerts different effects according to the type of previously administered substance (Prud'Homme et al., 2015). For example, preclinical studies indicated that CBD was able to reverse the conditioned place preference effect induced by synthetic THC, cocaine and amphetamine (Parker et al., 2004; Vann et al., 2008). Also, in alcohol- and cocaine-dependent rats CBD attenuated the drug seeking behaviour without inducing tolerance, sedation, or interfering with normal motivated behaviour (Gonzalez-Cuevas et al., 2018). In rodents, CBD chronic administration did not induce dependence whilst the long-term co-administration of equal ratios of CBD and THC did not reduce

THC dependence levels (Myers et al., 2018). In evaluating the role of oral CBD in frequent, healthy, cannabis users, Babalonis et al. (2017) found that CBD at 200, 400, 800 mg once daily (OD) was not associated with abuse when compared to oral placebo and active marijuana products with high levels of THC up to 5.3-5.8%. Conversely, the use of nabiximols (i.e. a combination of THC and CBD; trade name Sativex®) in a population of recreational cannabis users showed comparable abuse potential with dronabinol (i.e. the enantiomer (−)-trans-Δ9-tetrahydrocannabinol; trade names Marinol® and Syndros®) (Schoedel et al., 2011). No studies concerning the effect of the use of CBD alone in cannabis dependence were identified, although a case report of a 19-year-old woman successfully treated with CBD for the treatment of cannabis withdrawal syndrome has been described (Crippa et al., 2013). Furthermore, Turna et al. (2019) carried out a systematic review to assess the potential of CBD as a candidate pharmacotherapy for alcohol use disorder (AUD). Twelve papers met criteria for inclusion; 9 were preclinical and 3 focussed on healthy adult volunteers. In human studies, CBD was well tolerated and did not interact with the subjective effects of alcohol, hence CBD was suggested to have promise as a candidate AUD pharmacotherapy.
Finally, a neuroprotective role of CBD is suggested in cannabis users, by interfering with THC-induced hippocampal volume reduction (Yücel et al., 2017); improving memory (Morgan et al., 2010a); and reducing THC-associated depressive and psychotic-like symptoms (Morgan et al., 2008; Solowij et al., 2018).

Clinical trials

Only 6 completed clinical trials were identified, focusing on tobacco withdrawal (Hindocha et al., 2018); opioid (Hurd et al., 2015); and cannabis dependence (Allsop et al., 2014; Bhardwaj et al., 2018; Trigo et al., 2016a; Trigo et al., 2016b; Trigo et al., 2018).
Hindocha and collegues (2018) compared the effects of 800 mg oral CBD with placebo in dependent cigarette smokers after one night of abstinence. They found increased attentional bias levels to drug and food stimuli, considered a putative marker for drug cue salience during abstinence, in placebo but not in the CBD group. Although craving and withdrawal symptoms did not show any modification following CBD treament, the CBD group showed a reduction in explicit pleasantness levels of smoking-related images during abstinence when compared to placebo, a finding consistent with previous observations (Morgan et al., 2013).
In a double-blind pilot study, a small sample of opioid-dependent individuals who had been abstinent for at least 7 days were randomized to 3-day treatment with either CBD or placebo. Participants allocated to CBD showed attenuated subjective cue-induced craving up to 7 days after the end of treatment (Hurd et al., 2015), confirming previous preclinical suggestions (Ren et al., 2009).
A double-blind RCT (Allsop et al., 2014) compared a 6-day treatment with nabiximols oromucosal spray (THC 86.4 mg/CBD 80 mg) to placebo in cannabis-dependent inpatients during detoxification. Lower rates of dropouts, together with a significant reduction of withdrawal symptoms and craving, were found in the group treated with nabiximols. However, no differences between groups were found in relapse rates at the 28-day follow-up. Similar results were reported in a group of non-treatment seeker cannabis users (Trigo et al., 2016b). Indeed, in an 8-week pilot RCT, composed by four ‘smoke as usual’ conditions separated by four ‘cannabis abstinence’ periods, high doses of nabiximols (up to THC 108 mg/CBD 100 mg), were compared with placebo to assess its efficacy on withdrawal and craving symptoms. Both standard and low/self-titrated condition dosages were effective in reducing unpleasant withdrawal/craving symptoms. To better evaluate both efficacy and tolerability of self-titrated dosages of nabiximols on cannabis use, the same research team investigated as-needed treatment schedules (e.g up to THC 113.4 mg / CBD 105 mg daily) compared to placebo in a 12-week RCT (Trigo et al., 2018). Both groups received weekly Motivational Enhancement (MET) and

Cognitive Behavioural Therapy (CBT) sessions. Treatment with nabiximols exhibited effectiveness in reducing cannabis craving, with no serious adverse events reported. Despite this, no significant changes in abstinence rates were registered. Finally, a phase III trial on the use of nabiximols in cannabis dependent outpatients who had not previously responded to conventional psycho-social intervention is currently ongoing (Bhardwaj 2018). In this trial participants are being randomly allocated to CBD or placebo, in combination with six structured CBT sessions, for 12 weeks.

CBD and psychotic disorders

Background

The relationship between psychosis and cannabis use has been largely investigated. The acute use of cannabis could lead to the onset of a transient psychotic episode or heterogeneous psychotic-like symptoms (Favrat et al., 2005; Pierre et al., 2016; Thomas 1996). Furthermore, cannabis has been proposed as a risk factor for the development of schizophrenia, with higher risk associated with younger age at first use, frequency, and duration of use (Casadio et al., 2011; Di Forti et al., 2015; Hall and Degenhardt, 2008; Moore et al., 2007). Moreover, it has been shown that the risk of developing psychotic symptoms is associated with THC/CBD ratios (Di Forti et al., 2019). For instance, the high THC/low CBD level preparations, known as 'skunk', have been described as less safe compared with CBD-rich cannabis (Di Forti et al., 2015; Shubart et al., 2011). A longitudinal study, comparing three groups of volunteers identified by hair-sample analyses (i.e., THC+CBD users, THC-alone users, no THC/CBD users), showed that the THC-alone group presented with higher frequency of unusual experiences and anhedonia symptoms when compared to THC+CBD individuals (Morgan et al., 2008). However, it is unclear if CBD maintains its protective role also in heavy smokers or if this is limited to recreational users (Morgan et al., 2012). In animals, CBD presented with some effect on positive, negative and cognitive symptoms of schizophrenia models (Campos et al., 2017; Fakhoury 2016; Rohleder et al., 2016; Seeman 2016); however, this is still a much-debated topic (Zuardi et al., 2012).

It has been hypothesised that the overstimulation of CB1 receptor on GABAergic and glutamatergic neurons induced by frequent use of THC may modulate dopaminergic inputs to the striatum (Morrison and Murray, 2009), being involved in the onset of THC-induced psychosis. Moreover, the eCBS' hyperactivation might induce a dysregulation of the attentional salience processing systems (Bhattacharayya et al., 2012), which has been interpreted as a core alteration in the genesis of psychosis (Kapur 2003). Considering the putative eCBS involvement in the pathophysiology of schizophrenia (Ferretjans et al., 2012; Ligresti et al., 2016), CBD has been suggested to represent an effective and well-tolerated alternative treatment for schizophrenia (Diviant et al., 2018; Zuardi et al., 2006a) with a profile more similar to clozapine than to haloperidol (Crippa et al., 2015).

Initial suggestions for an atypical anti-psychotic profile of CBD derived from a single case report (Zuardi et al., 1995). CBD may be effective in schizophrenia both on its own (Zuardi et al., 2006b) and as an augmentation for antipsychotic therapy. In a case-control study, acute administration of CBD did not lead to any beneficial effects on cognitive performances of chronic schizophrenic patients (Hallak et al., 2010). To this respect, preclinical studies have suggested that the alleged pro-cognitive properties of chronic CBD administration could be associated with its anti-inflammatory and neuroprotective effects (Gomes et al., 2015; Hahn 2018). Pre-treatment with 600 mg of oral CBD in healthy individuals inhibited THC-induced paranoia and episodic memory impairment (Englund et al., 2013) but, in a recent case series (Schipper et al., 2018), the use of bedrolite (i.e. 0.4% THC and 9% CBD) in psychotic cannabis misusers failed to show efficacy in reducing both psychotic and drug withdrawal symptoms.

A few mechanisms have been hypothesised as a possible explanation for CBD potential anti-psychotic properties, including: facilitation of endocannabinoid signalling (Pisanti et al., 2017); partial agonist activity on dopamine D2 receptors, similarly to the atypical anti-psychotic aripiprazole (Seeman 2016); and activation of TRPV1 receptor pathways, which facilitates glutamate pre-synaptic release (Campos et al., 2012; Gururajan and Malone, 2016). Moreover, an increase of AEA levels in cerebrospinal fluid was documented as inversely correlated with both psychotic symptoms (Giuffrida et al., 2004) and frequency of cannabis use (Leweke et al., 2007). In comparison with healthy controls, higher blood levels of AEA have been found in patients with schizophrenia (Potvin et al., 2008). More recently, Minichino et al (2019) carried out a systematic review and meta-analysis of the blood and cerebrospinal fluid (CSF) measures of the eCBS in psychotic disorders. A total of 18 studies were included; higher eCBS tone levels were found at an early stage of illness in individuals who were antipsychotic naïve or free. This had an inverse association with symptom severity and was normalized after successful treatment. Although in some brain areas reduced levels of AEA may represent an adaptive mechanism counteracting hyperdopaminergic states (Fakhoury 2017; Giuffrida et al., 2004), CBD intake is associated with increased AEA levels (Leweke et al., 2012a), indirectly activating CB1 receptors (Campos et al., 2012; Rohleder et al., 2016). Overall, the exact mechanism underpinning the supposed beneficial CBD role in psychosis remains unclear (Leweke et al., 2012a; Arnold et al., 2012).

Clinical trials

The first RCT that explored CBD antipsychotic properties was a phase II, double-blind, study comparing CBD and amisulpride (both up to 800 mg/day) in a population of inpatients with schizophrenia during an acute exacerbation. After 4 weeks, both treatments showed similar efficacy in reducing the scores of the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS), but CBD was associated with fewer side effects. Higher levels of plasmatic AEA were found in subjects exposed to CBD compared to those exposed to amisulpride, with a statistically significant association between increase in AEA levels and decrease in psychotic symptoms in the first group (Leweke et al., 2012a). The same authors later performed a small cross-over clinical trial in antipsychotic-naïve patients with acute first-episode schizophrenia (Leweke et al., 2012b; Leweke et al. 2014a; Leweke et al., 2014b), receiving a 14-day treatment of 600mg CBD first followed by a 14-day placebo regimen or viceversa; a small and not statistically significant reduction in PANSS total scores was found. Currently, two RCTs evaluating CBD efficacy in both first episode of psychosis (FEP) (Leweke et al., 2018) and patients within the first 7 years from the onset of the psychotic illness (Ranganathan et al., 2018) are being carried out. The first study will focus on the efficacy of CBD versus placebo as an add-on of antipsychotic treatment in a cohort of 180 FEP patients. The latter will study the effects of CBD-alone on patients within 7 years from the onset of the psychosis; it will look at psychotic and cognitive symptoms, but also electrophysiological biomarkers and metabolic parameters.

The possible beneficial effect of CBD in chronic schizophrenia was explored in a recent multicentre RCT (McGuire et al., 2018a; McGuire et al., 2018b). Chronic, partial responder, psychotic patients were randomized to treatment with either CBD (1,000 mg/day) or placebo, as an augmentation to the usual anti-psychotic therapy. The CBD group showed a statistically significant reduction of positive, but not negative, symptoms compared to the placebo group. The cognitive tests were comparable in both groups, a finding consistent with previous evidence (Boggs et al., 2018b). Indeed, in a within-subject cross-over study of FEP patients, acute CBD administration of 600 mg was associated with a decreased activity in the left hippocampus and the right parahippocampal gyrus during a verbal recall task, suggesting a CBD modulatory effect on neural substrates underlying learning and memory

impairment in schizophrenia patients (O'Neill et al., 2018). In a double-blind RCT with 33 antipsychotic medication–naive participants at clinical high risk (CHR) of psychosis, Bhattacharayya et al. (2018a) found a reduced activation in the right caudate during encoding, and in the parahippocampal gyrus and midbrain during recall task, in CHRs compared to controls. Interestingly, a small innovative study used the virtual reality paradigm to test modification in paranoid ideation in a group of ultra-high risk (UHR) individuals after treatment with CBD for 7 days versus placebo (Bhattacharayya et al., 2016). Reduced scores of paranoia and anxiety, respectively evaluated with State Social Paranoia scale and State-Anxiety inventory-state subscale, were identified in the CBD group. Overall, sedation has been the only CBD side effect reported in the different studies (Boggs et al., 2018b; McGuire et al., 2018a; Leweke et al., 2012a).

CBD and anxiety disorders

Background

The eCBS is involved in the regulation of several physiological functions, including the emotional behaviour, which is in turn associated with both learning and response to emotionally salient events (Blessing et al., 2015; Schiavon et al., 2016). The CB1 receptor is involved in the response of acute stress and fear/anxiety response (Blessing et al., 2015). In preclinical studies, reduction in CB1 receptor signaling mediates the anxiogenic effects of corticotropin-releasing hormone in the amygdala (Gray et al., 2015), while its activation excites the negative feedback of the neuroendocrine stress response, hindering adverse effect of chronic stress (Evanson et al., 2010; Abush & Akirav, 2013).

CBD anxiolytic-like properties have been tested in several animal models, properties which are possibly being mediated by CBD action on postsynaptic 5-HT1A receptors (Lee et al., 2017; Campos et al., 2016; Ligresti et al., 2016; Blessing et al., 2015; Campos et al., 2012; Bergamaschi et al., 2011a; de Mello Schier et al., 2011). According to Lee et al (2017), there is accumulating preclinical evidence investigating the effects of CBD on fear memory processing indicating that it reduces learned fear in paradigms that are translationally, relevant to phobias. This may be associated with attenuation of the acute autonomic responses associated to stress (Fogaca et al., 2014; Fusar-Poli et al., 2009), whilst the extinction of fear memories will occur through indirect activation of CB1 receptors (Bitencourt et al., 2008; Lee et al, 2017). Other mechanisms associated with the anxiolytic properties of CBD may also include CBD-related modifications of the cerebral blood flow in limbic and paralimbic areas (Campos et al., 2012; Crippa et al., 2011).

Agents that target the eCBS directly (such as THC, CB1 agonists, and FAAH inhibitors) have shown a biphasic effect (e.g. low doses anxiolytic; higher doses anxiogenic; Parolaro et al, 2010). The use of cannabis is associated with dysphoria, anxiety and panic symptoms, especially with higher dose of THC (Parolaro et al., 2010). Conversely, CBD does not cause anxiety even at high dosages when administered in models of general anxiety (Bitencourt and Takahashi, 2018). In a double-blind study conducted on healthy volunteers exposed to the Simulated Public Speaking Test (SPST), a single dose of CBD 300 mg in powder form (99.9% purity), but not 150 or 600 mg, was identified as the optimal therapeutic dose when compared to placebo to treat SPST-induced anxiety (Linares et al., 2018a). In a double-blind placebo-controlled study, the effect of a single dose of CBD 300 mg was compared with two other anxiolytic compounds (ipsapirone 5 mg and diazepam 10 mg) in 40 healthy university students exposed to SPST. Ipsapirone was found to attenuate SPST-induced anxiety; CBD decreased anxiety after SPST; and diazepam was associated with significant sedative effects but had no effect in reducing the anxiety induced by the speech test (Zuardi et al., 1993). A putative anti-panic effects of

CBD have been hypotized (Soares and Campos, 2017), but no reliable evidence has been made available so far.
Finally, a few preclinical studies investigated chronic CBD intake in anxiety-related disorders. Mice exposed to chronic stress showed increased hippocampal proliferation levels after repeated CBD administration (Campos et al., 2013), suggesting that CBD pro-neurogenic activity may determine an anxiolytic effect by facilitating endocannabinoid-mediated signalling through CB1/CB2 receptors activation (Campos et al. 2013; Fogaça et al. 2018). This is consistent with the evidence that CBD could disrupt fear-memory consolidation by activation of dorsal hippocampus CB1/CB2 receptors, inducing a range of effects similar to those obtained with FAAH inhibitors' administration (Stern et al. 2017). However, the current evidence of an anxiolytic role of CBD in humans is largely limited to acute dosing only (Blessing et al., 2015).

Clinical trials

In our systematic review, only 2 relevant completed RCTs were identified. Both trials explored the efficacy of an acute administration of CBD on anxiety symptoms in a population of individuals with Social Anxiety Disorder (SAD). In a double-blind trial, 24 never-treated SAD patients were randomly allocated to receive either a pre-treatment single dose of CBD 600 mg or placebo and were compared to healthy controls following SPST exposure (Bergamaschi et al., 2011a). Pre-treatment of SAD patients with CBD 600 mg significantly inhibited the fear of speaking in public (i.e. reduction of anxiety, cognitive impairment and discomfort in speech performance; decreased alert in anticipatory speech) when compared to placebo. In a randomized, within-subject, cross-over design study, 10 treatment-naïve males with SAD were given either an oral dose of CBD 400 mg or placebo (Crippa et al., 2011). CBD was associated with significantly decreased levels in anxiety scores compared to placebo. To investigate the neural and behavioural effects of study medications, a technetium-99m-ethyl cysteinate dimer (99mTc-ECD) single-photon emission computed tomography (SPECT) was also carried out. Compared to placebo, CBD attenuated ECD uptake in an anatomical cluster encompassing the left parahippocampal gyrus and hippocampus, whilst it increased ECD uptake in the right posterior cingulate gyrus. Finally, a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of flexibly dosed CBD oil capsules versus placebo (Clinical Trials.gov, 2018a) is currently being carried out. The study involves 50 adults with a primary SAD; Generalized Anxiety Disorder (GAD); and Panic Disorder (PD). During the 8-week treatment, effects on symptoms and cognition as well as tolerability of CBD will be evaluated. Biological markers will also be collected to assess the relationship between inflammation, anxiety and CBD.

CBD and mood disorders

Background

The eCBS is known to play a role in mood regulation. Several animal studies have reported depressive symptoms, such as anhedonic state, passive coping behaviour and cognitive deficits in both rat models and CB1 knock-out mice (Martin et al., 2002; Rubino et al., 2008; Rubino et al., 2009). In a recent systematic review (Gibbs et al., 2015), it has been suggested the existence of an inverse relationship between cannabis use and clinical stability of bipolar disorder clients. Furthermore, antagonism at CB1 receptors with rimonabant has been associated with occurrence of depressive-like states (Moreira et al., 2009; Hill et al., 2005), whereas CBD has shown antidepressant and pro-hedonic effects in preclinical models (Zanelati et al., 2010; Shoval et al., 2016; El-Alfy et al., 2010; Sartim et al., 2016). The acute

antidepressant effect of CBD seems to depend on facilitation of the 5HT1A receptor-mediated neurotransmission, both directly and through CB1-receptor interaction (Sartim et al., 2016; Zanelati et al., 2010). In animal models, the above mechanism may be associated as well with increased extracellular 5-HT and glutamate levels in the ventromedial prefrontal cortex, which have been considered a possible explanation for the CBD-induced acute antidepressant effects (Linge et al., 2016; Micale et al., 2013). Furthermore, CBD may be associated with an indirect action in serotonin pathways through an elevation of triptophan levels (Jenny et al., 2010). Previous anecdotal reports on CBD monotherapy (with any dosage) in bipolar disorders have however failed to prove a beneficial effect for the treatment and management of manic episodes (Zuardi et al., 2010).

Clinical Trials

No completed clinical trials studying the role of CBD in mood disorders were identified. However, a project focusing on the effects of CBD in bipolar disorder is being carried out. This is a double-blind placebo-controlled RCT aiming at evaluating the efficacy of CBD 600 mg as augmentation therapy in bipolar patients during a depressive episode. CBD is hypothesized to produce a reduction of depressive and anxiety symptoms, together with an improvement in functioning and inflammatory biomarkers (Clinical Trials.gov, 2017a).

CBD and other psychiatric disorders

Neurocognitive disorders

Background

CBD interest in neurocognitive disorders is due to its reported antioxidant, anti-inflammatory, anti-apoptotic and neuroprotective properties (da Silva et al., 2018; Fernandez-Ruiz et al., 2013; Martin-Moreno et al., 2011; Mori et al., 2017; Osborne et al., 2017; Schiavon et al., 2014). It has been proposed that these effects could be more related to the CBD structure and stereochemistry rather than to its CB-receptor binding affinity (Aso et al., 2016b; Wu et al., 2013). CBD anti-inflammatory effects may improve outcomes also in some neurological acute disorders, such as meningitis or hepatic encephalopathy (Avraham et al., 2011; Barichello et al., 2012), and metabolic illnesses as diabetes-associated dementia (Brook et al., 2019). Moreover, in studies using Alzheimer dementia (AD)-mice models, CBD reduced both tau protein hyperphosphorylation (Aso et al., 2016a; Casajeros et al., 2013) and cerebral pro-inflammatory mechanisms, including production of interleukins and nitric oxide (Aso et al., 2013; Iuvone et al., 2009; Walther and Halpern, 2010). In mice, CBD could improve facial recognition (Cheng et al., 2014a; Cheng et al., 2014b) and memory (Fagherazzi et al., 2012; Wright et al. 2013), with a peculiar role in fear-associated, emotional, memory (Stern et al., 2018; Uhernik et al., 2018). However, Karl et al. (2017) warned that a better detailed preclinical characterization of CBD is required to understand the consequences of long-term CBD treatment and to analyse its potential side effects in an ageing organism.
CBD appeared to have beneficial effects on cognition compared to THC both in healthy controls and in cannabis users (Colizzi and Bhattacharyya, 2017; Englund et al., 2013; Morgan et al., 2010b; Morgan et al., 2012; Solowij et al., 2018). In a study involving a healthy population, a placebo CBD pre-treated group compared to a placebo pre-treated group resulted in both episodic and verbal memory tasks better performances after intravenous THC administration (Englund et al., 2013; Colizzi and

Bhattacharyya, 2017). Some 134 users were divided into high- and low-CBD cannabis groups (i.e. CBD/THC ratio respectively of 0.64 and 0.02) and were evaluated in terms of memory and psychotomimetic symptoms, both when on- and off-drug. Low-CBD cannabis consumption was associated with marked impairment in immediate and delayed prose recall (Morgan et al., 2010b). Furthermore, higher THC/CBD ratios may impact negatively on memory and psychological well-being (Morgan et al., 2012). Moreover, in daily cannabis users after a ten-week add-on trial of CBD 200 mg/day an improvement in attentional switching, verbal learning, and memory functioning was identified (Solowij et al., 2018).

Clinical Trials

Three eligible RCTs were here identified; one was carried out in Parkinson disease (PD) (Chagas et al., 2014) and two in Huntington disease (HD) patients (Consroe et al., 1991; Lopez-Sendon Moreno et al., 2016). In a double-blind RCT (Chagas et al., 2014) carried out in 21 PD patients, daily administration of CBD 300 mg was associated with an improvement of quality of life 'daily activity' domain. Data on drug-free HD patients did however not show either clinical or side effects after 6-week treatment with CBD (Consroe et al., 1991). In a more recent trial (Lopez-Sendon Moreno et al., 2016), no modification in functioning were detected in HD patients for any motor, cognitive or psychiatric measures after 12 weeks of THC/CBD combination therapy with Sativex® (2.7 mg THC/2.5 mg CBD per spray).

Sleep disorders

Background

Evidence suggests that the eCBS modulation may have a role in the treatment of sleep disorders (SDs) (National Academies of Sciences, Engineering, and Medicine, 2017; Sachs et al., 2015). In several animal studies, reduction of eCBS activity led to increased waking while its activation enhanced sleep in rodents (Murillo-Rodríguea et al., 2016).

CBD has shown to possess a dual effect on sleep latency, i.e. it is associated with decreasing time to sleep onset at low dosages and increasing time at high dosages (Babson et al., 2017; National Academies of Sciences, Engineering, and Medicine, 2017; Zuardi et al., 2008). CBD may possibly act on circadian clock genes and melatonin production (Lafaye et al., 2018). Moreover, preclinical intracerebral perfusion of CBD could prevent sleep rebound after total sleep deprivation (Murillo-Rodriguez et al., 2011) and increase wakefulness in the lights-on period, supporting a clinical alerting effect for this agent in managing somnolence (Babson et al., 2017; Murillo-Rodriguez et al., 2006; Scuderi et al., 2009). On the other hand, CBD-induced sedation has been shown both in animal and human studies, supposedly because of a corticotropin releasing hormone (CRH)-related gene downregulation (Lafaye et al., 2018; Russo et al., 2007). In a study using a PTSD-mice model, CBD microinjected in amygdala both reduced anxiety and reversed REM blockage associated with anxiety (Hsiao et al., 2012). However, acute administration of CBD 300 mg in healthy volunteers did not interfere with volunteers' sleep-wake cycle (Linares et al., 2016).

Carlini and Cunha (1981) first provided evidence of a sedative effect of CBD in a healthy population. CBD (primarily nabiximols) may improve short-term sleep outcomes in patients with SDs secondary to obstructive sleep apnoea, fibromyalgia, chronic pain, or multiple sclerosis (National Academies of Sciences, Engineering, and Medicine, 2017). The anecdotal use of cannabis derivatives for insomnia and parasomnia is largely widespread (Chagas et al., 2014; Vigil et al., 2018). Naturalistic data on adult

patients showed a major subjective relief from insomnia with CBD but not with THC (Vigil et al., 2018; Belendiuk et al., 2015). CBD oil has been anecdotally reported to be effective in treating PTSD-related resistant insomnia in a 10-year old girl (Shannon and Oplia-Lehman, 2016). Despite the above anecdotal suggestions, the role of CBD in SDs is still unclear. In a large retrospective case-series, CBD failed to show a sustained improvement during a 3-month trial involving individuals with sleep problems (Shannon et al., 2019). These inconsistent findings could either be due to different CBD dosages being ingested (Zhornitsky and Potin, 2012); or to CBD concurrent administration with THC (Nicholson et al., 2004, Pivik et al., 1972). In a recent RCT (Linares et al., 2018b), 27 healthy volunteers were selected and allocated to receive either CBD 300 mg or placebo; the acute oral administration of CBD did however not induce any effect in either sleep-wake cycle regulation or sleep architecture.

Clinical trials

No related RCTs were identified.

Personality traits and disorders

Background

The therapeutic use of CBD in personality disorders (PDs) has only partially been explored. Conversely, there have been suggestions of an association of some personality traits, such as novelty and sensation seeking (WHO, 2018), with the recreational use of cannabis.

Clinical trials

In a double-blind, placebo controlled, crossover design trial, variations in facial emotion recognition/emotional processing were compared in 48 individuals with high and low levels of frequency of cannabis use and schizotypal personality traits. Participating subjects were administered with inhaling THC (8mg); CBD (16 mg); THC+CBD (8 mg+16 mg); and placebo. Improvements in facial emotion recognition after CBD administration for both high and low schizotypy groups were identified; moreover, CBD attenuated the impairment induced by THC (Hindocha et al., 2015).

Eating disorders

Background

The medical use of Marinol® (dronabinol), a synthetically derived THC preparation, has been approved in 1985 to relieve resistant nausea and vomiting associated with chemotherapy in cancer patients, and in 1992 for inducing appetite in AIDS-related cachexia. Similarly, Nabilone® (a synthetic cannabinoid that mimics THC) was also approved in 1985 for improving the nausea of cancer chemotherapy (Marco et al., 2011; Horn et al., 2018). Rimonabant®, an anorectic antiobesity drug acting as an antagonist on CB1 receptors previously approved for the treatment of both obesity and metabolic syndrome, was withdrawn in 2008 worldwide due to serious psychiatric side effects (Waterlow and Chrisps, 2007). Overall, no sufficient literature levels supporting the use of cannabinoids as beneficial for eating disorders (EDs) have been identified (Marco et al., 2011). THC and other components of marijuana may contribute to the impact of cannabis on appetite and weight

(National Academies of Sciences, Engineering, and Medicine, 2017). In murine models, however, CBD reduced food intake both alone and in combination with other cannabinoid-derivatives (Farrimond et al., 2012, Riedel et al., 2009). In rat models, concurrent administration of leptin and CBD did not suppress appetite or reduce body weight gain (Wierucka-Rybak et al., 2014).

Clinical trials

No related RCTs were identified.

Obsessive-Compulsive Disorder (OCD)

Background

The anxiolytic effects of CBD (Crippa et al., 2018; de Mello-Schier et al., 2012) may be of use when considering some OCD-related clinical issues (Blessing et al., 2015; Crippa et al., 2018). Potentiation of AEA-mediated neurotransmission may be associated with the anti-compulsive, increased extinction, and impaired reconsolidation of aversive memories activities, together with facilitation of adult hippocampal neurogenesis (Campos et al., 2012). Considering the CBD-associated modulation of serotonergic neurotransmission (Campos et al., 2016; Lee et al., 2017; de Mello Schier et al., 2011), which is *per se* involved in the pathophysiology of OCD, assessing the use of CBD in animal models of compulsive behaviour is clearly of interest. In the marble-burying test (MBT) OCD preclinical model, CBD showed to be effective in decreasing the number of buried marbles, a finding consistent with a potential role of CBD in controlling compulsive behaviour (Casarotto et al., 2010; Deaiana et al., 2012). Moreover, CBD showed anti-compulsive effects on repetitive burying induced by meta-chlorophenyl-piperazine (mCPP) (Nardo et al., 2014).

Clinical trials

No related RCTs were identified.

Traumatic and Stress-related Disorders

Background

Post-traumatic stress disorder (PTSD) may develop as a maladaptive response after experiencing a potentially traumatic event (American Psychiatric Association, 2013; Bitencourt and Takahashi, 2018; Elms et al., 2018; Jurkus et al., 2016). The eCBS' dysregulation may predispose to the development of stress-related disorders (Heitland et al., 2012; Hill et al., 2018; Korem et al., 2016; Lisboa et al., 2018). In fact, eCBs are implicated in stress response, limbic system functioning and the hypothalamic–pituitary–adrenal axis modulation: all mechanisms putatively associated with PTSD development (Hill et al., 2018). Inhibition of the eCBS could lead to an increased activity of stress-related systems, ultimately causing chronic effects (Evanson et al., 2010; Abush & Akirav, 2013; Gray et al., 2015). Hence, CBD may exert its therapeutic effect on PTSD through the inhibition of either the reuptake or the enzymatic degradation of endogenous cannabinoids (Bitencourt and Takahashi, 2018; Berardi et al., 2016).
Marijuana may improve some PTSD symptoms, including sleep difficulty and anxiety, whilst facilitating increased extinction of aversive memories (Crippa et al., 2018; Elms et al., 2018; Greer et

al., 2014; Parolaro et al., 2010). Indeed, drugs acting on the eCBS may possess a dual ability to modulate both memory processes and reduce anxiety/depression (Crippa et al., 2011; Berardi et al., 2018). It is of interest that CBD agonism at 5HT1A receptors occurs in brain areas associated with defensive responses, including dorsal periaqueductal grey, bed nucleus of the stria terminalis, and medial prefrontal cortex (Campos et al., 2012; Crippa et al., 2011; Crippa et al., 2018; Mandolini et al. 2018; Marinho et al., 2015; Pisanti et al., 2017).

CBD was reported to reduce learned fear levels whilst acutely reducing fear expression, disrupting memory reconsolidation, and enhancing the process of psychological extinction (Berardi et al., 2016; Jurkus et al., 2016), features all relevant to PTSD. Consistent with this, Das et al. (2013), exposed 48 healthy human subjects to a fear-conditioning paradigm (i.e. brief electric shocks as unconditioned stimuli) in a double-blind, placebo-controlled trial with inhaled CBD 32 mg; they found that CBD enhanced consolidation of explicit fear extinction and attenuation of explicit fearful responding. Furthermore, a retrospective case series examined the effect of open-label oral CBD in 11 PTSD adult patients (Elms et al., 2018), that concurrently were receiving a pharmacological treatment and a psychotherapy during a period of 8 weeks. CBD showed to be effective, decreasing PTSD symptom severity in 91% (n = 10) of the total sample. Further, nabilone was observed to improve PTSD symptoms such as nightmares and daytime flashbacks (Berardi et al., 2016)

Clinical trials

To date, no RCTs evaluating the efficacy of CBD in reducing symptoms of PTSD have been completed. However, three ongoing trials were identified. The first one (Clinical Trials.gov, 2016) is a placebo-controlled crossover study focusing on both safety and efficacy of 4 different potencies of smoked CBD-containing marijuana, up to 1.8 grams per day and for a three-week period, administered to 76 veterans with chronic PTSD. Weekly evaluations include measures of symptoms of PTSD, depression, anxiety, sleep quality, suicidal ideation, general functioning, and responses to cannabis. A second ongoing study (Clinical Trials.gov, 2017b) aims at determining the effecacy of CBD in treating 50 patients with moderate/severe alcohol use disorder comorbid with PTSD. Patients are being randomized to treatment with either oral CBD 400 mg daily or placebo for a period of 6 weeks. The researchers will assess whether CBD treatment leads to a greater improvement in alcohol intake relative to placebo, and whether reduction in alcohol drinking is temporally linked to improvement in PTSD symptoms. A third study (Clinical Trials.gov, 2018b) has been designed to test the efficacy of CBD+Prolonged Exposure therapy (PE) versus PE+placebo for the treatment of PTSD in 136 veterans.

Dissociative Disorders

Background

The use of CBD in dissociative disorders (DDs) has not yet been explored. However, a case report described the effectiveness of CBD use in a subject with cannabis dependence and a history of cannabis withdrawal syndrome (Crippa et al., 2013). After ten days of daily CBD treatment, all significant withdrawal, anxiety and dissociative symptoms improved. In a double-blind placebo-controlled study, the effects of CBD and ketamine were investigated in a sample of 10 male healthy subjects (Hallak et al., 2011). Ketamine was administered by intravenous infusion (bolus of 0.26 mg/kg/1 min followed by IV infusion of 0.25 mg/kg over 30 minutes), preceded by either CBD (600 mg) or placebo. Results included an increase of ketamine activating effects, and a non-significant trend to reduce ketamine-

induced depersonalisation/derealisation dissociation symptoms, suggesting a complex interaction between CB1/CB2 and N-Methyl-D-Aspartate receptor systems.

Clinical trials

No related RCTs were here identified.

Somatic Disorders

Background

The use of cannabinoids has been suggested for the treatment of a range of somatic conditions, such as chronic pain, glaucoma, nausea/vomiting, sleep disorders, and Tourette syndrome (Whiting et al., 2015). Conversely, given the CBD neuroprotective, antiepileptic, analgesic, anti-inflammatory, anti-asthmatic, and antitumor properties, the molecule may possess a putative role in a large range of medical disorders (Pisanti et al., 2017). A recent review described the beneficial use of CBD in many common subjective pain syndromes having in common a symptomatology of hyperalgesia and central sensitisation, such as migraine and fibromyalgia (Russo, 2016). Finally, studies in both animal models and human volunteers seemed to show a therapeutic potential of cannabinoids in subjects affected by irritable bowel syndrome (National Academies of Sciences, Engineering, and Medicine, 2017). These effects may be due to the cannabinoid action on CB1 receptors in the colon mucosa and neuromuscular layers, ultimately inhibiting gastric/small intestinal transit and colonic propulsion/motility.

Clinical trials

No related RCTs were identified.

Discussion and conclusions

To the best of our knowedge, the present paper constitutes the most extensive and detailed systematic review specifically focussing on the evaluation of efficacy and safety of CBD in psychiatric populations. Recently, the therapeutic potential of drugs modulating the activity of endocannabinoid receptors has attracted significant interest (Chye et al., 2019; van der Flier et al., 2019; Przetsch et al., 2019). CBD use has been proposed for many medical issues for which it has not been studied (White et al, 2019). Conversely, levels of evidence relating to cannabinoids' efficacy for the treatment of chronic pain (Dzierzanowski 2019), chemotherapy-induced nausea (Mortimer et al., 2019), and multiple sclerosis spasticity symptoms (Torres-Moreno et al., 2018; National Academies of Sciences, Engineering, and Medicine, 2017) are largely reported. Cannabinoids' use for psychiatric diseases is still unclear. Given the availability of a range of high CBD/low THC experimental preparations (Solowji et al., 2019), 8 registered major clinical trials, focusing on a range of psychopathological conditions, are currently ongoing and a further one (Hurd et al, 2019), completed after the current paper deadline for data collection, has been published. Current data suggested that CBD showed some efficacy in the treatment of cannabis withdrawal symptoms, although its effect on craving seems limited to the acute phase. A few of the trials here commented reported as well some efficacy in the treatment of psychotic symptoms in both early-course and chronic schizophrenia, but not in cognitive

performance improvement. Finally, pre-administration of CBD seemed to reduce performance-related anxiety onset, a finding however suggested to be promising but not proven (White et al, 2019). Indeed, for the remaining psychopathological conditions here examined (e.g. mood; neurocognitive; sleep; personality; eating; obsessive-compulsive; trauma stress; dissociative; and somatic disorders) relating data resulted to be either inconclusive or, in agreement with White et al (2019), still overall weak. In parallel with this, there is increasing, but still preliminary, interest in CBD as monotherapy or add-on treatment for the core symptoms and co-morbidities of autistic spectrum disorders (Polek et al, 2019). Encouraging open label trials' results have recently been made available (Barchel et al, 2019) and, at present, many related RCTs are being carried out worldwide (Premoli et al, 2019).

Despite the limited number of RCTs, the interest in CBD and CBD-enriched preparations as promising psychotropic agents is growing, partially substained from preclinical and observational studies (Khoury et al., 2017). However, due to the limited number of available RCTs and the elevate heterogeneity between both studied populations and treatment characteristics (e.g. formulation, dosing, duration), an overall interpretation on the role of CBD in the psychiatric disorders is far to be clear.

Overall, with CBD administration no side effects other than sedation has been reported throughout the studies. However, further study to assess its impact on suicidal ideation are needed, and the risk of gastrointestinal adverse events; possible alteration in liver function tests; and drug interactions have recently been emphasized (White et al, 2019). Indeed, there are still a range of uncertainties regarding CBD sourcing, long-term safety, and CBD use in special categories, such as children, elderly and patients with degenerative and medical disorders (e.g., cardiovascular disease, renal and hepatic impairment; Fasinu et al., 2016; Khoury et al., 2017).

Finally, because of the peculiar pharmacodynamics and psychotropic properties of CBD and eCBS complexity (Szkudlarek et al., 2019), its potential addictive and abuse profile needs to be further assessed. Indeed, very recent studies suggested that CBD may well show some intoxicating properties when compared to placebo (Solowji et al., 2019). Furthermore, CBD low dosages combined with THC seem to enhance the intoxicating effects of THC, whilst high doses of CBD may reduce them (Solowji et al., 2019). In line with this, a range of CBD-related pre-marketing activities should be facilitated and implemented. Indeed, guidelines have been drafted to carry out laboratory-based testing to improve medications' abuse predictive ability (for a thorough overview of the issue, see Schifano et al., 2016). Abuse liability-focused laboratory testing may need to consider interaction studies of CBD with alcohol and/or other drugs. Consistent with remaining central nervous system active compounds, pharmaceutical manufacturers applying for approval of novel molecules such as CBD should consider submitting post-marketing plans for a strategy addressing education, prevention, detection and abuse/diversion issues. Finally, CBD post-authorization safety studies to monitor the effectiveness of any risk minimization measures should be drafted as well (Schifano et al., 2016).

Limitations and Conclusions

Current work presents with some limitations. First, potentially eligible studies might have been missed. To minimise this risk, a wide search strategy was performed on three international databases, together with a backward search from the reference lists of included studies. Again, recruited participants in trials focusing on the same disease presented heterogenous characteristics such as both stage (e.g. early-stage or chronic condition; low- and high-risk individuals), and state (i.e. acute or stable) of the disease being considered. Furthermore, CBD administration also varied in terms of formulation and dose and it is likely that the different CBD formulation used across studies could have resulted in different CBD plasma levels, which may have pharmacodynamics and pharmacokinetic implications. Also, due to the relative paucity of the studies here examined and the heterogeneity of both the

examined populations and of the single RCTs it was not possible to provide here conclusive information on concurrent medication use; drug plasma levels relevant to clinical effects; and also drug drug interactions.
Interventional studies with purified CBD are warranted, with a call to target-engagement proof-of-principle studies using the research domain criteria framework (Rong et al, 2017). Larger-scale, placebo-controlled, clinical studies are needed as well to investigate the effects of CBD as an adjunct to psychological therapy (Papagianni et al, 2019). In summary, further large-scale RCTs are required to better evaluate the efficacy of CBD in both acute and chronic illnesses, special categories, as well as to exclude any possible abuse liability.

References

Abush H, Akirav I. Cannabinoids ameliorate impairments induced by chronic stress to synaptic plasticity and short-term memory. Neuropsychopharmacology. 2013; 38:1521-34. doi: 10.1038/npp.2013.51

Adams R, Hunt M, Clark JH. Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. J Am Chem Soc. 1940; 62:196–200.

Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiatry. 2014; 71(3):281-91.

American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders (5th Edition). Arlington, VA: American Psychiatric Publishing.

Arnold JC, Boucher AA, Karl T. The yin and yang of cannabis-induced psychosis: the actions of Δ(9)-tetrahydrocannabinol and cannabidiol in rodent models of schizophrenia. Curr Pharm Des. 2012; 18(32):5113-30.

Aso E, Juvés S, Maldonado R, Ferrera I. CB2 cannabinoid receptor agonist ameliorates Alzheimer-like phenotype in A aPP/PS1 mice. J Alzheimer Dis. 2013; 35:847-58.

Aso E, Andrés-Benito P, Ferrera I. Delineating the Efficacy of a Cannabis-Based Medicine at Advanced Stages of Dementia in a Murine Model. J Alzheimer Dis. 2016a; 54:903-12. doi:10.3233/JAD-160533.

Aso E, Andrés-Benito P, Carmona M, Maldonado R, Ferrera I. Cannabinoid Receptor 2 Participates in Amyloid-β Processing in a Mouse Model of Alzheimer's Disease but Plays a Minor Role in the Therapeutic Properties of a Cannabis-Based Medicine. J Alzheimers Dis. 2016b; 51(2):489-500.

Avraham Y, Grigoriadis N, Poutahidis T, Vorobiev L, Magen I, Ilan Y, et al. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. Br J Pharmacol. 2011; 162(7):1650-8.

Babalonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. Drug Alcohol Depend. 2017; 172:9-13.

Babson KA, Sottile J, Morabito D. Cannabis, Cannabinoids, and Sleep: a Review of the Literature. Curr Psychiatry Rep. 2017; 19(4):23.

Barichello T, Ceretta RA, Generoso JS, Moreira AP, Simões LR, Comim CM, et al. Cannabidiol reduces host immune response and prevents cognitive impairments in Wistar rats submitted to pneumococcal meningitis. Eur J Pharmacol. 2012; 697(1-3):158-64.

Barchel D, Stolar O, De-Haan T, Ziv-Baran T, Saban N, Fuchs DO, Koren G, Berkovitch M. Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities. Front Pharmacol. 2019 Jan 9;9:1521. doi: 10.3389/fphar.2018.01521.

Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacol. 2010; 35(3):764-74.

Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S, Fusar-Poli P, et al. Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012; 69(1):27-36.

Bhattacharyya S, Appiah-Kus Ei, Wilson R, Hird A, Bossong M, Valmaggia L, et al. Effect of Cannabidiol on Paranoid Ideation in a Virtual Reality Environment in Individuals at Ultra High Risk of Psychosis. Oral Abstracts - 2016 - Early Intervention in Psychiatry.

Bhattacharyya S, Wilson R, Appiah-Kusi E, O'Neill A, Brammer M, Perez J, et al. Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. JAMA Psychiatry. 2018a; 75(11):1107-17.

Bhattacharyya S, Wilson R, Allen P, Bossong M, Appiah-Kusi E, McGuire P. Effect of cannabidiol on symptoms, distress and neurophysiological abnormalities in clinical high-risk for psychosis patients: a placebo-controlled study. Schizophr Bull. 2018b; 44(Suppl 1):S28.

Belendiuk KA, Babson KA, Vandrey R, Bonn-Miller MO. Cannabis species and cannabinoid concentration preference among sleep-disturbed medicinal cannabis users. Addict Behav. 2015; 50:178-81.

Berardi A, Schelling G, Campolongo P. The endocannabinoid system and Post Traumatic Stress Disorder (PTSD): From preclinical findings to innovative therapeutic approaches in clinical settings. Pharmacol Res. 2016; 111:668-78.

Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacol. 2011a; 36(6):1219-26.

Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 2011b; 6(4):237-49.

Bhardwaj AK, Allsop DJ, Copeland J, McGregor IS, Dunlop A, Shanahan M, et al. Agonist Replacement for Cannabis Dependence (ARCD) study group. Randomised Controlled Trial (RCT) of cannabinoid replacement therapy (Nabiximols) for the management of treatment-resistant cannabis dependent patients: a study protocol. BMC Psychiatry. 2018; 18(1):140.

Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. 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. 2001; 134(4):845-52.

Bitencourt RM, Pamplona FA, Takahashi RN. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur Neuropsychopharmacol. 2008; 18:849-59.

Bitencourt RM, Takahashi RN. Cannabidiol as a therapeutic alternative for post-traumatic stress disorder: From bench research to confirmation in human trials. Front Neurosci. 2018; 12:502.

Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a Potential Treatment for Anxiety Disorders. Neurotherapeutics. 2015; 12(4):825-36.

Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M. Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ9-Tetrahydrocannabinol. Neuropsychopharmacology. 2018a; 43(1):142-54.

Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia: a randomized placebo-controlled trial. Psychopharmacology. 2018b; 235(7):1923-32.

Brook E, Mamo J, Wong R, Al-Salami H, Falasca M, Lam V. Blood-brain barrier disturbances in diabetes-associated dementia: Therapeutic potential for cannabinoids. Pharmacol Res. 2019; 141:291-7.

Campos AC, Guimarães FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology. 2008; 199(2):223-30.

Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FC. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Phil Trans R Soc B. 2012; 367:3364-78.

Campos AC, Ortega Z, Palazuelos J, Fogaça MV, Aguiar DC, Díaz-Alonso J, et al. The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system. Int J Neuropsychopharmacol. 2013; 16(6):1407-19.

Campos AC, Fogaça MV, Sonego AB, Guimarães FS. Cannabidiol, neuroprotection and neuropsychiatric disorders. Pharmacol Res. 2016; 112:119-27.

Campos AC, Fogaça MV, Scarante FF, Joca SRL, Sales AJ, Gomes FV, et al. Plastic and Neuroprotective Mechanisms Involved in the Therapeutic Effects of Cannabidiol in Psychiatric Disorders. Front Pharmacol. 2017; 23(8):269.

Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol. 1981; 21(S1):417S-427S.

Carroll CB, Bain PG, Teare L, Liu X, Joint C, Wroath C, et al. Cannabis for dyskinesia in parkinson disease: A randomized double-blind crossover study. Neurology. 2004; 63:1245-50.

Casadio P, Fernandes C, Murray RM, Di Forti M. Cannabis use in young people: the risk for schizophrenia. Neurosci Biobehav. 2011; 35:1779–87.

Casarejos MJ, Perucho J, Gomez A, Muño MP, Fernandez-Estevez M, Sagredo O, Fernandez Ruiz J, et al. Natural Cannabinoids Improve Dopamine Neurotransmission and Tau and Amyloid Pathology in a Mouse Model of Tauopathy. J Alzheimer Dis. 2013; 35(3):525-39.

Casajuana Köguel C, López-Pelayo H, Balcells-Olivero MM, Colom J, Gual A. Psychoactive constituents of cannabis and their clinical implications: a systematic review. Adicciones. 2018; 30(2):140-51.

Casarotto PC, Gomes FV, Resstel LB, Guimarães FS. Cannabidiol inhibitory effect on marble-burying behaviour: involvement of CB1 receptors. Behav Pharmacol. 2010; 21(4):353-8.

Chagas MHN, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. J Psychopharmacol. 2014; 28(11):1088-98.

Cheng D, Spiro AS, Jenner AM, Garner B, Karl T. Long-Term Cannabidiol Treatment Prevents the Development of Social Recognition Memory Deficits in Alzheimer's Disease Transgenic Mice. J Alzheimer Disease. 2014a; 42(4):1383-96.

Cheng D, Low JK, Logge W, Garner B, Karl T. Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1ΔE9 mice. Psychopharmacology. 2014b; 231(15):3009-17.

Chye Y, Christensen E, Solowij N, Yücel M. The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder. Front Psychiatry. 2019; 10:63. Doi:10.3389/fpsyt.2019.00063.

Clinical Trials.gov, 2007. NCT00588731. Cannabidiol Treatment of Cognitive Dysfunction in Schizophrenia. Available from: https://clinicaltrials.gov/show/nct00588731 [Accessed: 15-Mar-2019].

Clinical Trials.gov, 2008. Evaluation of the Antipsychotic Efficacy of Cannabidiol in Acute Schizophrenic Psychosis. Available from: https://clinicaltrials.gov/show/nct00628290 [Accessed: 15-Mar-2019].

Clinical Trials.gov, 2016. NCT02759185. Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With PTSD. Available from: https://clinicaltrials.gov/show/nct02759185 [Accessed: 15-Mar-2019].

Clinical Trials.gov, 2017a. NCT03310593. Cannabidiol as an Adjunctive Treatment for Bipolar Depression. Available from: https://clinicaltrials.gov/show/nct03310593 [Accessed: 15-Mar-2019].

Clinical Trials.gov, 2017b. NCT03248167. Cannabidiol as a Treatment for AUD Comorbid With PTSD. Available from: https://clinicaltrials.gov/show/nct03248167 [Accessed: 15-Mar-2019].

Clinical Trials.gov, 2018a. NCT03549819. Cannabidiol for the Treatment of Anxiety Disorders: an 8-Week Pilot Study. Available from: https://clinicaltrials.gov/show/nct03549819 [Accessed: 15-Mar-2019].

Clinical Trials.gov, 2018b. NCT03518801. Cannabidiol and Prolonged Exposure. Available from: https://clinicaltrials.gov/show/nct03518801 [Accessed: 15-Mar-2019].

Colizzi M, Bhattacharyya S. Does Cannabis Composition Matter? Differential Effects of Delta-9-tetrahydrocannabinol and Cannabidiol on Human Cognition. Curr Addict Rep. 2017; 4(2):62-74.

Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. Controlled clinical trial of cannabidiol in huntington's disease. Pharmacol Biochem Behav. 1991; 40:701-8.

Corroon J, Phillips JA. A Cross-Sectional Study of Cannabidiol Users. Cannabis Cannabinoid Res. 2018; 3(1):152-61.

Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran F, Martin-Santos R, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol. 2011; 25(1):121-30.

Crippa JA, Hallak JE, Machado-de-Sousa JP, Queiroz RH, Bergamaschi M, Chagas MH, et al. Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. J Clin Pharm Ther. 2013; 38(2):162-4.

Crippa JA, Hallak JE, Abílio VC, de Lacerda AL, Zuardi AW. Cannabidiol and Sodium Nitroprusside: Two Novel Neuromodulatory Pharmacological Interventions to Treat and Prevent Psychosis. CNS Neurol Disord Drug Targets 2015; 14(8):970-8.

Crippa JA, Guimarães FS, Campos AC, Zuardi AW. Translational Investigation of the Therapeutic Potential of Cannabidiol (CBD): Toward a New Age. Front Immunol. 2018; 9:2009.

da Silva VK, de Freitas BS, Carvalho Lacerda Garcia R, Tavares Monteiro R, Hallak JE, Zuardi AW, et al. Antiapoptotic effects of cannabidiol in an experimental model of cognitive decline induced by brain iron overload. Transl Psychiatry. 2018; 8(1):176.

Das RK, Kamboj SK, Ramadas M, Yogan K, Gupta V, Redman E, et al. Cannabidiol enhances consolidation of explicit fear extinction in humans. Psychopharmacology. 2013; 226:781-2.

Deiana S, Watanabe A, Yamasaki Y, Amada N, Arthur M, Fleming S, et al. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Δ(9)-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behaviour. Psychopharmacology. 2012; 219(3):859-73.

de Mello Schier AR, de Oliveira Ribeiro N, de Oliveira Silva AC, Hallak JEC, Crippa JAS, Nardi AE, et al. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. Rev Bras Psiquiatr. 2012; 34(Supl1):S104-17.

Devane WA, Hanus L, Breuer A. Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992; 258(5090):1946-9.

Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry. 2015; 2(3):233-8.

Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al. EU-GEI WP2 Group. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry. 2019 Mar 19. pii: S2215-0366(19)30048-3.

Diviant JP, Vigil JM, Stith SS. The Role of Cannabis within an Emerging Perspective on Schizophrenia. Medicines. 2018; 5(3):86.

Dzierżanowski T. Prospects for the Use of Cannabinoids in Oncology and Palliative Care Practice: A Review of the Evidence. Cancers. 2019; 11(2).

El-Alfy AT, Ivey K, Robinson K, Ahmed S, Radwan M, Slade D, et al.: Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L. Pharmacol Biochem Behav. 2010; 95:434-42.

Elmes MW, Kaczocha M, Berger WT, Leung K, Ralph BP, Wang L, et al. Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). J Biol Chem. 2015; 290(14):8711-21.

Elms L, Shannon S, Hughes S, Lewis N. Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series. J Altern Complement Med. 2018 Dec 13.

Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 2013; 27(1):19-27.

Evanson NK, Tasker JG, Hill MN, Hillard CJ, Herman JP. Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling. Endocrinology. 2010; 151:4811-9. Doi: 10.1210/en.2010-0285

Fakhoury M. Could cannabidiol be used as an alternative to antipsychotics? J Psychiatr Res. 2016; 80:14-21.

Fakhoury M. Role of the Endocannabinoid System in the Pathophysiology of Schizophrenia. Mol Neurobiol. 2017; 54(1):768-78.

Fagherazzi EV, Garcia VA, Maurmann N, Bervanger T, Halmenschlager LH, Busato SB, et al. Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders. Psychopharmacology. 2012; 219(4):1133-40.

Farrimond JA, Whalley BJ, Williams CM. Cannabinol and cannabidiol exert opposing effects on rat feeding patterns. Psychopharmacology. 2012; 223(1):117-29.

Fasinu PS, Phillips S, ElSohly MA, Walker LA. Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Agents. Pharmacotherapy. 2016; 36(7):781-96.

Favrat B, Ménétrey A, Augsburger M, Rothuizen LE, Appenzeller M, Buclin T, Pin M, Mangin P, Giroud C. Two cases of "cannabis acute psychosis" following the administration of oral cannabis. BMC Psychiatry. 2005; 5:17.

Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? Br J Clin Pharmacol. 2013; 75(2):323-33.

Ferretjans R, Moreira FA, Teixeira AL, Salgado JV. The endocannabinoid system and its role in schizophrenia: a systematic review of the literature. Braz J Psychiatr. 2012; 34(Suppl 2):S163-77.

Fogaca MV, Reis FM, Campos AC, Guimaraes FS. Effects of intra-prelimbic prefrontal cortex injection of cannabidiol on anxiety-like behavior: involvement of 5HT1A receptors and previous stressful experience. Eur Neuropsychopharmacol. 2014; 24:410-9.

Fogaça MV, Campos AC, Coelho LD, Duman RS, Guimarães FS. The anxiolytic effects of cannabidiol in chronically stressed mice are mediated by the endocannabinoid system: Role of neurogenesis and dendritic remodeling. Neuropharmacology. 2018; 135:22-33.

Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, et al. Distinct effects of Δ9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry. 2009; 66(1):95-105.

Gibbs M, Winsper S, Marwaha E, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: A systematic review and meta-analysis. J Affect Disord. 2015; 171:39-47.

Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, et al. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacol. 2004; 29(11):2108-14.

Gomes FV, Llorente R, Del Bel EA, Viveros MP, López-Gallardo M, Guimarães FS. Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol. Schizophr Res. 2015; 164(1-3):155-63.

Gonzalez-Cuevas G, Martin-Fardon R, Kerr TM, Stouffer DG, Parsons LH, Hammell DC, et al. Unique treatment potential of cannabidiol for the prevention of relapse to drug use: preclinical proof of principle. Neuropsychopharmacol. 2018; 43(10):2036-45

Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, et al. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacol. 2004; 29(11):2108-14.

Gray JM, Vecchiarelli HA, Morena M, Lee TTY, Hermanson CJ, Kim AB, et al. Corticotropin-releasing hormone drives anandamide hydrolysis in the amygdala to promote anxiety. J Neurosci. 2015; 35:3879-92. Doi: 10.1523/JNEUROSCI.2737-14.2015

Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. J Psychoactive Drugs. 2014; 46(1):73-7.

Gururajan A, Malone DT. Does cannabidiol have a role in the treatment of schizophrenia? Schizophr Res. 2016; 176(2-3):281-90.

Hahn B. The potential of Cannabidiol Treatment for cannabis users with Recent-Onset Psychosis Schizophr Bull. 2018; 44(1):46-53.

Hall W, Degenhardt L. Cannabis use and the risk of developing a psychotic disorder. World Psychiatry. 2008; 7(2):68-71.

Hallak JE, Machado-de-Sousa JP, Crippa JA, Sanches RF, Trzesniak C, Chaves C, et al. Performance of schizophrenic patients in the Stroop Color Word Test and electrodermal responsiveness after acute administration of cannabidiol (CBD). Braz J Psychiatry. 2010; 32(1):56-61.

Hallak JEC, Dursun SM, Bosi DC, Horta de Macedo LR, Machado-de-Sousa JP, Abrao J, et al. 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. 2011; 135(1):198-202.

Heitland I, Klumpers F, Oosting RS, Evers DJJ, Leon Kenemans J, Baas JMP. Failure to extinguish fear and genetic variability in the human cannabinoid receptor 1. Transl Psychiatry. 2012; 2:e162.

Hill MN, Gorzalka BB. Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression? Behav Pharmacol. 2005; 16:333-52.

Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther. 2012; 133(1):79-97.

Hill MN, Campolongo P, Yehuda R, Patel S. Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder. Neuropsychopharmacol. 2018; 43(1):80-102.

Hindocha C, Freeman TP, Schafer G, Gardener C, Das RK, Morgan CJA, et al. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A

randomised, double- blind, placebo-controlled study in cannabis users. Eur Neuropsychopharmacol. 2015; 25(3):325-34.

Hindocha C, Freeman TP, Grabski M, Stroud JB, Crudgington H, Davies AC, et al. Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal. Addiction 2018; 113(9):1696-705.

Horn H, Böhme B, Dietrich L, Koch M. Endocannabinoids in Body Weight Control. Pharmaceuticals (Basel). 2018;11(2):55.

Hsiao YT, Yi PL, Li CL, Chang FC. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. Neuropharmacology. 2012; 62(1):373-84.

Hurd YL, Yoon M, Manini AF, Hernandez S, Olmedo R, Ostman M, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. Neurotherapeutics. 2015; 12:807-15.

Hurd YL, Spriggs S, Alishayev J, Winkel G, Gurgov K, Kudrich C, Oprescu AM, Salsitz E. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. Am J Psychiatry. 2019 May 21:appiajp201918101191. doi: 10.1176/appi.ajp.2019.18101191. [Epub ahead of print]

Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders? CNS Neurosci Ther. 2009 Winter; 15(1);65-75.

Jenny M, Schröcksnadel S, Überall F, Fuchs D. The Potential Role of Cannabinoids in Modulating Serotonergic Signaling by Their Influence on Tryptophan Metabolism. Pharmaceuticals. 2010; 3(8):2647-60.

Jurkus R, Day HLL, Guimarães FS, Lee JLC, Bertoglio LJ, Stevenson CW. Cannabidiol regulation of learned fear: implications for treating anxiety-related disorders. Front Pharmacol. 2016; 7:454.

Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry. 2003; 160(1):13-23.

Karl T, Garner B, Cheng D. The therapeutic potential of the phytocannabinoid cannabidiol for Alzheimer's disease. Behav Pharmacol. 2017; 28 (2 and 3-Spec Issue):142-60.

Khoury JM, Neves MCLD, Roque MAV, Queiroz DAB, Corrêa de Freitas AA, de Fátima Â, Moreira FA, Garcia FD. Is there a role for cannabidiol in psychiatry? World J Biol Psychiatry. 2017; 20:1-16.

Korem N, Zer-Aviv TM, Ganon-Elazar E, Abush H, Akirav I. Targeting the endocannabinoid system to treat anxiety-related disorders. J Basic Clin Physiol Pharmacol. 2016; 27(3):193-202.

Lafaye G, Karila L, Blecha L, Benyamina A. Cannabis, Cannabinoids and Health. Dialogues Clin Neurosci. 2017; 19(3):309-16.

Lafaye G, Desterke C, Marulaz L, Benyamina A. Cannabidiol affects circadian clock core complex and its regulation in microglia cells. Addict Biol. 2018 Oct 11. Doi: 10.1111/adb.12660.

Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015; 172(20):4790-805.

Lee D, Milman G, Barnes AJ, Goodwin RS, Hirvonen J, Huestis MA. Oral fluid cannabinoids in chronic, daily Cannabis smokers during sustained, monitored abstinence. Clin Chem. 2011; 57(8):1127-36.

Lee JLC, Bertoglio LJ, Guimarães FS, Stevenson CW. Cannabidiol regulation of emotion and emotional memory processing: relevance for treating anxiety-related and substance abuse disorders. Br J Pharmacol. 2017 Oct;174(19):3242-3256. doi: 10.1111/bph.13724.

Leweke FM, Giuffrida A, Koethe D, Schreiber D, Nolden BM, Kranaster L, et al. Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use. Schizophr Res. 2007; 94(1-3):29-36.

Leweke FM. Anandamide dysfunction in prodromal and established psychosis. Curr Pharm Des. 2012; 18(32):5188-93.

Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2012a; 2:e94.

Leweke FM, Hellmich M, Kranaster L, Koethe D. Cannabidiol as a new type of an antipsychotic: results from a placebo-controlled clinical trial. Biological Psychiatry. 2012b; 71(8, Supp 1):63S.

Leweke FM, Rohleder C, Falkai P, Heinz A, Klosterkotter J, Schneider F, et al. Enhancing recovery in early schizophrenia - A controlled clinical trial investigating cannabidiol CR versus. placebo as an add-on to antipsychotic treatment. Early Intervention in Psychiatry. 2014a; 8(Suppl. S1), Seiten/Artikel-Nr.:Symposia, 20-20.

Leweke FM, Rohleder C, Enning F, Pahlisch F, Schaefer C, Mueller JK, et al. A homeostatic role for the endocannabinoid system in schizophrenia. IJNP. 2014b; 17:14.

Leweke FM, Rohleder C, Müller JK, Hirjak D, Meyer-Lindenberg A. Cannabidiol zur Verbesserung der Genesung in frühen Stadien einer Schizophrenie. Eine randomisierte, kontrollierte klinische Prüfungder adjuvanten Gabe zur individuellen antipsychotischen Behandlung. Nervenheilkunde. 2018; 37(05):319-23.

Ligresti A, De Petrocellis L, Di Marzo V. From Phytocannabinoids to Cannabinoid Receptors and Endocannabinoids: Pleiotropic Physiological and Pathological Roles Through Complex Pharmacology. Physiol Rev. 2016; 96(4):1593-659.

Linares I, Guimaraes FS, Eckeli A, Zuardi AW, Souza JDS, Hallak JEC, et al. Lack of cannabidiol effects on sleep-wake cycle in healthy patients. Eur Neuropsychopharmacol. 2016; 26(2):S369.

Linares I, Zuardi AW, Pereira LC, Hallak JEC, Queiroz RHC, Guimarães FS, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. Eur Neuropsychopharmacol. 2018a; 26:S617.

Linares IMP, Guimaraes FS, Eckeli A, Crippa ACS, Zuardi AW, Souza JDS, et al. No Acute Effects of Cannabidiol on the Sleep-Wake Cycle of Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study. Front Pharmacol. 2018b; 9:315.

Linge R, Jiménez-Sánchez L, Campa L, Pilar-Cuéllar F, Vidal R, Pazos A, et al. Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. Neuropharmacology. 2016; 103:16-26.

Lisboa SF, Vila-Verde C, Rosa J, Uliana DL, Stern CA, Bertoglio LJ, et al. Tempering aversive/traumatic memories with cannabinoids: a review of evidence from animal and human studies. Psychopharmacology. 2019; 236(1):201-26.

López-Sendón Moreno JL, García Caldentey J, Trigo Cubillo P, Ruiz Romero C, García Ribas G, Alonso Arias MA, et al. A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease. J Neurol. 2016; 263(7):1390-400.

Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. Biol Psychiatry. 2016; 79(7):516-25.

Mandolini GM, Lazzaretti M, Pigoni A, Oldani L, Delvecchio G, Brambilla P. Pharmacological properties of cannabidiol in the treatment of psychiatric disorders: a critical overview. Epidemiol Psychiatr Sci. 2018; 27(4):327-35.

Mannucci C, Navarra M, Calapai F, Spagnolo EV, Busardò FP, Cas RD, et al. Neurological Aspects of Medical Use of Cannabidiol. CNS Neurol Disord Drug Targets. 2017; 16(5):541-53.

Marco EM, García-Gutiérrez MS, Bermúdez-Silva FJ, Moreira FA, Guimarães F, Manzanares J, et al. Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects. Front Behav Neurosci. 2011;5:63.

Marinho AL, Vila-Verde C, Fogaça MV, Guimarães FS. Effects of intra-infralimbic prefrontal cortex injections of cannabidiol in the modulation of emotional behaviors in rats: contribution of $5HT_1A$ receptors and stressful experiences. Behav Brain Res. 2015; 286:49-56.

Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O. Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology. 2002; 159:379-7.

Martín-Moreno AM, Reigada D, Ramírez BG, Mechoulam R, Innamorato N, Cuadrado ML, et al. Cannabidiol and Other Cannabinoids Reduce Microglial Activation In Vitro and In Vivo: Relevance to Alzheimer's Disease. Mol Pharmacol. 2011; 79(6):964-73.

McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry. 2018a; 175(3): 225-31.

McGuire P, Robson P, Cubała W, Vasile D, Morrison P, Barron R, et al. A randomized controlled trial of cannabidiol in schizophrenia. Schizoph Bull. 2018b; 44(Supp 1):S27.

Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science. 1970; 169 (3945):611-2.

Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. Endocannabinoid system and mood disorders: priming a target for new therapies. Pharmacol Ther. 2013; 138(1):18-37.

Minichino A, Senior M, Brondino N, Zhang SH, Godwlewska BR, Burnet PWJ, Cipriani A, Lennox BR. Measuring Disturbance of the Endocannabinoid System in Psychosis: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2019 Jun 5. doi: 10.1001/jamapsychiatry.2019.0970. [Epub ahead of print]

Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7):e1000097.

Moore THM, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007; 370(9584):319-28.

Moreira FA, Crippa JA. The psychiatric side-effects of rimonabant. Rev Bras Psiquiatr. 2009; 31:145-53.

Morgan CJ, Gardener C, Schafer G, Swan S, Demarchi C, Freeman TP, et al. Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychol Med. 2012; 42(2):391-400.

Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry. 2008; 192(4):306-7.

Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology. 2010a; 35(9):1879-85.

Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. Br J Psychiatry. 2010b; 197(4):285-90.

Morgan CJ, Das RK, Joye A, Curran HV, Kamboj SK. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. Addict Behav. 2013; 38(9):2433-6.

Mori MA, Meyer E, Soares LM, Milani H, Guimarães FS, de Oliveira RMW. Cannabidiol reduces neuroinflammation and promotes neuroplasticity and functional recovery after brain ischemia. Prog Neuropsychopharmacol Biol Psychiatry. 2017; 75:94-105.

Morrison PD, Murray RM. From real-world events to psychosis: the emerging neuropharmacology of delusions. Schizophr Bull Jul 35(4): 668–674. Doi: 10.1093/schbul/sbp049.

Mortimer TL, Mabin T, Engelbrecht AM. Cannabinoids: the lows and the highs of chemotherapy-induced nausea and vomiting. Future Oncol. 2019 Feb 5.

Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colín R. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. FEBS. 2006; 580(18):4337-45.

Murillo-Rodríguez E, Palomero-Rivero M, Millán-Aldaco D, Mechoulam R, Drucker-Colín R. Effects on sleep and dopamine levels of microdialysis perfusion of cannabidiol into the lateral hypothalamus of rats. Life Sci. 2011; 88(11-12):504-11.

Murillo-Rodríguez E, Machado S, Rocha NB, Budde H, Yuan TF, Arias-Carrión O. Revealing the role of the endocannabinoid system modulators, SR141716A, URB597 and VDM-11, in sleep homeostasis. Neuroscience. 2016; 339:433-9. Doi: 10.1016/j.neuroscience.2016.10.011.

Myers AM, Siegele PB, Foss JD, Tuma RF, Ward SJ. Single and combined effects of plant-derived and synthetic cannabinoids on cognition and cannabinoid-associated withdrawal signs in mice. Br J Pharmacol. 2018 Jan 16.

Nardo M, Casarotto PC, Gomes FV, Guimaraes FS. Cannabidiol reverses the mCPP-induced increase in marble-burying behaviour. Fundam Clin Pharmacol. 2014; 28(5):544-50.

National Academies of Sciences, Engineering, and Medicine 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press (US).

Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of D-9-Tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J Clin Psychopharmacol. 2004; 24(3):305.

Noel C. Evidence for the use of "medical marijuana" in psychiatric and neurologic disorders. Ment Health Clin. 2018; 7(1):29-38.

O'Neill A, Wilson R, Appiah-Kusi E, Bossong M, McGuire P, Bhattacharyya S. Effects of cannabidiol on mediotemporal and dorsostriatal activity during encoding and recall, in the at-risk mental state for psychosis. Schizoph Bull. 2017; 43(Supp 1):S187.

O'Neill A, Wilson R, Blest-Hopley G, Annibale L, Colizzi M, Bhattacharyya S. Cannabidiol induced modulation of mediotemporal activity during a verbal memory task in first-episode psychosis. Schizophr Bull. 2018; 44(Supp 1):S384.

Osborne AL, Solowij N, Weston-Green K. A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia. Neurosci Biobehav Rev. 2017; 72:310-24.

Papagianni EP, Stevenson CW. Cannabinoid Regulation of Fear and Anxiety: an Update. Curr Psychiatry Rep. 2019 Apr 27;21(6):38. doi: 10.1007/s11920-019-1026-z.

Parker LA, Burton P, Sorge RE, Yakiwchuk C, Mechoulam R. Effect of low doses of delta9-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats. Psychopharmacology. 2004; 175:360-6.

Parolaro D, Realini N, Vigano D, Guidali C, Rubino T. The endocannabinoid system and psychiatric disorders. Exp Neurol. 2010; 224(1):3-14.

Pierre JM, Gandal M, Son M. Cannabis-induced psychosis associated with high potency "wax dabs." Schizoph Res. 2016; 172(1-3):211-2.

Pisanti S, Malfitano AM, Ciaglia E, Lamberti A, Ranieri R, Cuomo G, et al. Cannabidiol: State of the art and new challenges for therapeutic applications. Pharmacology & Therapeutics. 2017; 175:133-50.

Pivik RT, Zarcone V, Dement WC, Hollister LE. Delta-9-tetrahydrocannabinol and synhexl: effects on human sleep patterns. Clin Pharmacol Ther. 1972; 13(3):426-35.

Poleg S, Golubchik P, Offen D, Weizman A. Cannabidiol as a suggested candidate for treatment of autism spectrum disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2019 Mar 8;89:90-96. doi: 10.1016/j.pnpbp.2018.08.030.

Potvin S, Kouassi E, Lipp O, Bouchard RH, Roy MA, Demers MF, et al. Endogenous cannabinoids in patients with schizophrenia and substance use disorder during quetiapine therapy. J Psychopharmacol. 2008; 22(3):262-9.

Premoli M, Aria F, Bonini SA, Maccarinelli G, Gianoncelli A, Pina SD, Tambaro S, Memo M, Mastinu A. Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment. Life Sci. 2019 May 1;224:120-127. doi: 10.1016/j.lfs.2019.03.053. Epub 2019 Mar 22

Pretzsch CM, Freyberg J, Voinescu B, Lythgoe D, Horder J, Mendez MA, et al. Effects of cannabidiol on brain excitation and inhibition systems; a randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder. Neuropsychopharmacol. 2019 Feb 6.

Prud'homme M, Cata R, Jutras-Aswad D. Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence. Subst Abuse. 2015; 9:33-8.

Ranganathan M, D'Souza D, Cortes-Briones J, Skosnik P. Efficacy of cannabidiol in the treatment of early psychosis. Schizoph Bull. 2018; 44(Suppl 1):S27.

Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J Neurosci 2009 Nov 25;29(47):14764-9.

Riedel G, Fadda P, McKillop-Smith S, Pertwee RG, Platt B, Robinson L. Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice. Br J Pharmacol. 2009; 156(7):1154-66.

Rodríguez-Muñoz M, Sánchez-Blázquez P, Merlos M, Garzón-Niño J. Endocannabinoid control of glutamate NMDA receptors: the therapeutic potential and consequences of dysfunction. Oncotarget. 2016; 7(34):55840-62.

Rohleder C, Müller JK, Lange B, Leweke FM. Cannabidiol as a Potential New Type of an Antipsychotic. A Critical Review of the Evidence. Front Pharmacol. 2016; 7:422.

Rong C, Lee Y, Carmona NE, Cha DS, Ragguett RM, Rosenblat JD, et al. Cannabidiol in medical marijuana: Research vistas and potential opportunities. Pharmacol Res. 2017; 121:213-8.

Rubino T, Vigano D, Realini N, Guidali C, Braida D, Capurro V, et al. Chronic delta 9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical correlates. Neuropsychopharmacol. 2008; 33:2760-71.

Rubino T, Realini N, Braida D, Alberio T, Capurro V, Vigano D, et al. The depressive phenotype induced in adult female rats by adolescent exposure to THC is associated with cognitive impairment and altered neuroplasticity in the prefrontal cortex. Neurotox. Res.2009; 15:291-302.

Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. Chem Biodivers. 2007; 4(8):1729-43.

Russo EB. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in Migraine, Fibromyalgia, Irritable Bowel and other treatment-resistant syndromes. Cannabis Cannabinoid Res. 2016; 1(1):154-65.

Sachs J, McGlade E, Yurgelun-Todd D. Safety and Toxicology of Cannabinoids. Neurotherapeutics. 2015; 12(4):735-46.

Sartim AG, Guimarães FS, Joca SR. Antidepressant-like effect of cannabidiol injection into the ventral medial prefrontal cortex-Possible involvement of 5-HT1A and CB1 receptors. Behav Brain Res. 2016; 303:218-27.

Scherma M, Masia P, Deidda M, Fratta W, Tanda G, Fadda P. New Perspectives on the Use of Cannabis in the Treatment of Psychiatric Disorders. Medicines. 2018; 5(4).

Schiavon AP, Soares LM, Bonato JM, Milani H, Guimarães FS, Weffort de Oliveira RM. Protective effects of cannabidiol against hippocampal cell death and cognitive impairment induced by bilateral common carotid artery occlusion in mice. Neurotox Res. 2014; 26(4):307-16.

Schiavon AP, Bonato JM, Milani H, Guimarães FS, Weffort de Oliveira RM. Influence of single and repeated cannabidiol administration on emotional behavior and markers of cell proliferation and neurogenesis in non-stressed mice. Prog Neuropsychopharmacol Biol Psychiatry. 2016; 64:27-34.

Schifano F, Papanti GD, Orsolini L, Corkery JM. The consequences of drug misuse on post-marketing surveillance. Expert Review of Clinical Pharmacology. 2016; 9(7):867-71.

Schipper R, Dekker M, de Haan L, van den Brink W. Medicinal cannabis (Bedrolite) substitution therapy in inpatients with a psychotic disorder and a comorbid cannabis use disorder: A case series. J Psychopharmacol. 2018; 32(3):353-6.

Schoedel KA, Chen N, Hilliard A, White L, Stott C, Russo E, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. Hum Psychopharmacol. 2011; 26(3):224-36.

Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr Res. 2011; 130(1-3):216-21.

Scuderi C, Filippis DD, Iuvone T, Blasio A, Steardo A, Esposito G. Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders. Phytother Res. 2009; 23(5):597-602.

Seeman P. Cannabidiol is a partial agonist at dopamine D2High receptors, predicting its antipsychotic clinical dose. Transl Psychiatry. 2016; 6(10):e920.

Shannon S, Oplia-Lehman J. Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of posttraumatic stress disorder: A case report. Perm J. 2016; 20:108-11.

Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. Perm J. 2019; 23. pii:18-041.

Shbiro L, Hen-Shoval D, Hazut N, Rapps K, Dar S, Zalsman G, et al. Effects of cannabidiol in males and females in two different rat models of depression. Physiol Behav. 2019; 201:59-63. doi: 10.1016/j.physbeh.2018.12.019.

Shoval G, Shbiro L, Hershkovitz L, Hazut N, Zalsman G, Mechoulam R, et al. Prohedonic Effect of Cannabidiol in a Rat Model of Depression. Neuropsychobiology. 2016;7 3(2):123-9.

Solowij N, Broyd SJ, Beale C, Prick JA, Greenwood LM, van Hell H, et al. Therapeutic Effects of Prolonged Cannabidiol Treatment on Psychological Symptoms and Cognitive Function in Regular Cannabis Users: A Pragmatic Open-Label Clinical Trial. Cannabis Cannabinoid Res. 2018;3(1):21-34.

Soares VP, Campos AC. Evidences for the Anti-panic Actions of Cannabidiol. Curr Neuropharmacol. 2017; 15(2):291-9.

Solowij N, Broyd S, Greenwood LM, van Hell H, Martelozzo D, Rueb K, et al. A randomised controlled trial of vaporised Δ9-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects. Eur Arch Psychiatry Clin Neurosci. 2019; 269(1):17-35. Doi: 10.1007/s00406-019-00978-2.

Stern CAJ, de Carvalho CR, Bertoglio LJ, Takahashi RN. Effects of Cannabinoid Drugs on Aversive or Rewarding Drug-Associated Memory Extinction and Reconsolidation. Neuroscience. 2018; 370:62–80.

Stern CAJ, da Silva TR, Raymundi AM, de Souza CP, Hiroaki-Sato VA, Kato L, Guimarães FS, et al. Cannabidiol disrupts the consolidation of specific and generalized fear memories via dorsal hippocampus CB1 and CB2 receptors. Neuropharmacology. 2017; 125:220-30.

Szkudlarek HJ, Desai SJ, Renard J, Pereira B, Norris C, Jobson CEL, et al. Δ-9-Tetrahydrocannabinol and Cannabidiol produce dissociable effects on prefrontal cortical executive function and regulation of affective behaviors. Neuropsychopharmacol. 2019; 44(4):817-25.

Thomas H. A community survey of adverse effects of cannabis use. Drug Alcohol Depend. 1996; 42(3):201-7.

Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol. 2007; 150(5):613-23.

Torres-Moreno MC, Papaseit E, Torrens M, Farré M. Assessment of efficacy and tolerability of medicinal cannabinoids in patients with multiple sclerosis: a systematic review and meta-analysis. JAMA Netw Open. 2018; 1(6):e183485.

Trigo JM, Lagzdins D, Rehm J, Selby P, Gamaleddin I, Fischer B, et al. Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. Drug Alcohol Depend. 2016a; 161:298-306.

Trigo JM, Lagzdins D, Rehm J, Selby P, Gamaleddin I, Fischer B, et al. Effects of fixed or self-titrated dosages of Sativex on cannabis users. Drug Alcohol Depend. 2016b; 161:298-306.

Trigo JM, Soliman A, Quilty LC, Fischer B, Rehm J, Selby P, et al. Nabiximols combined with motivational enhancement/cognitive behavioural therapy for the treatment of cannabis dependence: A pilot randomized clinical trial. PLoS One. 2018; 13(1):e0190768.

Turna J, Syan SK, Frey BN, Rush B, Costello MJ, Weiss M, et al. Cannabidiol as a Novel Candidate Alcohol Use Disorder Pharmacotherapy: A Systematic Review. Alcohol Clin Exp Res. 2019 Jan 30. Doi: 10.1111/acer.13964.

Uhernik AL, Montoya ZT, Balkissoon CD, Smith JP. Learning and memory is modulated by cannabidiol when administered during trace fear-conditioning. Neurobiol Learn Mem. 2018; 149:68-76.

van der Flier FE, Kwee CMB, Cath DC, Batelaan NM, Groenink L, Duits P, et al. Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias: study protocol of a randomized controlled trial. BMC Psychiatry. 2019; 19(1):69.

Vann RE, Gamage TF, Warner JA, Marshall EM, Taylor NL, Martin BR, et al. Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Delta(9)-tetrahydrocannabinol. Drug Alcohol Depend. 2008; 94:191-8.

Vigil JM, Stith SS, Diviant JP, Brockelman F, Keeling K, Hall B. Effectiveness of Raw, Natural Medical Cannabis Flower for Treating Insomnia under Naturalistic Conditions. Medicines. 2018; 5(3).

Walther S, Halpern M. Cannabinoids and Dementia: A Review of Clinical and Preclinical Data. Pharmaceuticals. 2010; 3(8):2689-708.

Ware MA, Tawfik VL. Safety issues concerning the medical use of cannabis and cannabinoids. Pain Res Manag. 2005; 10(Supp A):31A-37A.

Waterlow M, Chrisp P. Rimonabant: the evidence for its use in the treatment of obesity and the metabolic syndrome. Core Evid. 2008;2(3):173-87.

White CM. A Review of Human Studies Assessing Cannabidiol's (CBD) Therapeutic Actions and Potential. J Clin Pharmacol. 2019 Jul;59(7):923-934. doi: 10.1002/jcph.1387. Epub 2019 Feb 7.

Wierucka-Rybak M, Wolak M, Bojanowska E. The effects of leptin in combination with a cannabinoid receptor 1 antagonist, AM 251, or cannabidiol on food intake and body weight in rats fed a high-fat or a free-choice high sugar diet. J Physiol Pharmacol. 2014; 65(4):487-96.

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use. A Systematic Review and Meta-analysis. JAMA. 2015; 313(24):2456-73.

World Health Organisation (2018). The health and social effects of nonmedical cannabis use. Available from: https://www.who.int/substance_abuse/publications/cannabis_report/en/ [Accessed: 21-Feb-2019].

Wright MJ Jr, Vandewater SA, Taffe MA. Cannabidiol attenuates deficits of visuospatial associative memory induced by Δ(9) tetrahydrocannabinol. Br J Pharmacol. 2013;170(7):1365-73.

Wu J, Bie B, Yang H, Xu JJ, Brown DL, Naguib M. Activation of the CB(2) receptor system reverses amyloid- induced memory deficiency. Neurobiol Aging. 2013; 34(3):791-804.

Xi ZX, Peng XQ, Li X, Song R, Zhang H, Liu QR, et al. Brain cannabinoid CB(2) receptors modulate cocaine's actions in mice. Nat Neurosci. 2011; 14:1160-6.

Yücel M, Lorenzetti V, Suo C, Zalesky A, Fornito A, Takagi MJ, et al. Hippocampal harms, protection and recovery following regular cannabis use. Transl Psychiatry. 2016; 6:e710.

Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. Br J Pharmacol. 2010; 159(1):122-8.

Zhang HY, Gao M, Liu QR, Bi GH, Li X, Yang HJ, et al. Cannabinoid CB2 receptors modulate midbrain dopamine neuronal activity and dopamine- related behavior in mice. Proc Natl Acad Sci U S A. 2014; 111:E5007-E5015.

Zhornitsky S, Potvin S. Cannabidiol in humans—the quest for therapeutic targets. (2012) Pharmaceuticals. 2012; 5(5):529-52.

Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology. 1982; 76:245-50.

Zuardi AW, Cosme RA, Graeff FG, Guimarães FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. J Psychopharmacol. 1993; 7(Supp 1):82-8.

Zuardi AW, Morais SL, Guimarães FS, Mechoulam R. Antipsychotic effect of cannabidiol. J Clin Psychiatry. 1995; 56(10):485-6.

Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res. 2006a; 39(4):421-9.

Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE, et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol. 2006b; 20(5):683-6.

Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Braz J Psychiatr. 2008; 30(3):271-80.

Zuardi AW, Crippa J, Dursun S, Morais S, Vilela J, Sanches R, et al. Cannabidiol was ineffective for manic episode of bipolar affective disorder. J Psychopharmacol. 2010; 24(1):135-7.

Zuardi AW, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, et al. A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. Curr Pharm Des. 2012; 18(32):5131-40.