AN UNBIASED EVALUATION OF THE POTENTIAL BENEFITS OF CANNABIS IN NEUROPSYCHIATRIC CONDITIONS

ABSTRACT

BACKGROUND: Cannabis has been proposed to have efficacy in treating a range of neuropsychiatric conditions. Therefore, it is justified to systematically review the literature to evaluate this claim.

METHODS: The therapeutic potential of cannabinoids in neuropsychiatric conditions was investigated, following PRISMA guidelines. Studies assessing the potential benefits of cannabis and related compounds in the treatment of neuropsychiatric conditions were searched in the PubMed database up until March 2020. The risk of bias was also assessed.

RESULTS: The initial search identified 3112 results of which 23 clinical trials were included. The strongest evidence is for cannabidiol (CBD) as an adjunct in acute psychosis and schizophrenia. There is evidence for cannabidiol in the treatment of anxiety, nabilone for PTSD-related sleep disturbance and tetrahydrocannabinol (THC) for tic reduction.

CONCLUSION: The review showed that there is limited evidence regarding the efficacy of cannabinoids in the treatment of neuropsychiatric disorders. Future large-scale randomised double-blind controlled trials with longitudinal assessment and standardised methodology are needed to gather stronger evidence for the use of cannabis in treating neuropsychiatric conditions.

INTRODUCTION

Cannabis is one of the most widely used drugs in the world (UNODC, 2016). Positive acute effects include euphoria and relaxation, while adverse effects include anxiety and paranoia (Curran *et al.*, 2016). Cannabis contains 133 known phytocannabinoids, with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most abundant (Pertwee, 2006).

THC is the principal psychoactive component of cannabis and exerts its effects through partial agonism on type 1 endocannabinoid receptors (CB_1R). THC has also been demonstrated to modulate anxiety, increase fear extinction and impair facial emotional processing (Hindocha *et al.*, 2015). CBD has a complex pharmacology which includes inverse agonism of cannabinoids receptors, enzyme inhibition, and neurotransmitter modulation (Thomas et al., 2007). Cannabinoid receptors are mainly expressed in key brain regions of relevance to neuropsychiatric disorders including the amygdala, frontal lobes and basal ganglia (Glass et al., 1997). As such, the endocannabinoid system (eCBS) is involved in several neurocognitive domains also of importance to neuropsychiatric disorders including reward, emotional and memory processing (Mechoulam and Parker, 2013). There is evidence that the eCBS is involved in the pathophysiology of a range of psychiatric disorders and promising clinical evidence of a therapeutic role of cannabis in psychiatry (Fattore, 2015).

The use of cannabinoids in neuropsychiatry has been considered controversial and the evidence for its potential therapeutic effects is largely underdeveloped. As decriminalisation and legalisation of cannabis has spread, research into therapeutic use of cannabinoids and the role of the eCBS in psychopathology has increased. It is thus timely for an updated systematic review, focusing on high quality clinical evidence, to be conducted.

The included neuropsychiatric disorders account for leading global causes of morbidity and mortality. In each condition a subtherapeutic response is common and side effects are often not well tolerated (Pallanti *et al.*, 2002). For example, dopamine antagonists – used in treatment-refractory obsessive-compulsive disorder, psychosis and Tourette's syndrome, are associated with deleterious metabolic and extrapyramidal side effects

(Bloch *et al.*, 2006; Huys *et al.*, 2012). In addition, around 30% of patients on dopamine antagonists do not respond and the majority of responders relapse within a few years (Emsley *et al.*, 2013). For each condition, a summary of initial evidence supporting a therapeutic role of cannabinoids will be given, followed by results obtained from a systematic review. The main objective of this review is to evaluate the potential benefits of cannabis in the treatment of a range of neuropsychiatric disorders.

METHODS

SEARCH STRATEGY

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The PubMed database was searched and references in reviews were also screened to examine relevant studies. An electronic search was performed using the following Boolean input "(cannab* OR canab* OR marijuana OR nabiximol OR THC OR CBD OR tetrahydrocannabinol OR nabilone OR dronabinol) AND (antidepress* OR neuropsychiatric OR depression OR depressive OR anxiety OR psychosis OR psychiatric OR psychotic OR "affective disorder" OR "mental illness" OR bipolar OR schizophren* OR psychosis OR OCD OR "obsessive compulsive" OR obsessive-compulsive OR PTSD OR post-traumatic OR "post traumatic" OR ADHD OR "attention deficit" OR phobi* OR psychiat* OR "attention-deficit" OR touret* OR tic)" and clinical trials and reviews were filtered. Items published up to March 2020 were included.

SCREENING AND ELIGIBILITY

Titles and abstracts were screened for relevance then the full text was read. Then, the reference lists of systematic reviews and included studies identified in the initial search were screened to identify any additional studies that met the inclusion criteria. The inclusion criteria were as follows: (1) Reviews or placebo-controlled clinical trials assessing the potential benefit of cannabis or cannabinoids in the treatment of depression, anxiety, OCD, ADHD, schizophrenia, psychosis, BAD, Tourette's syndrome, (2) Placebo-controlled clinical trials assessing the potential benefit of cannabis or cannabinoids in drug-induced symptoms of aforementioned conditions. The exclusion criteria were as follows: (1) case reports, (2) non-intervention studies (3) retrospective or cross-sectional studies; (4) in vivo and animal studies; (5) studies of mental health symptoms only as secondary outcomes; (6) studies not written in English; (7) conference abstracts.

DATA EXTRACTION (Table A)

The following data was extracted into a table: author, drug and dose, length of treatment, type of study, number of participants, primary outcome, diagnosis, control, outcome, key findings and level of evidence (Oxford Center for Evidence-based Medicine-Levels of Evidence guideline; (Phillips, 2014).

RISK OF BIAS ASSESSMENT (Table B)

Risk of bias was assessed using the Cochrane Risk of Bias tool for RCTs (Higgins *et al.*, 2019). Eligible studies were assessed using seven criteria: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants, (4) personnel and outcomes, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. With each criterion, the risk of bias was rated as either "low" or "high". If there was insufficient information to decide, it was rated as "unclear".

RESULTS

The search of the electronic database generated 3112 results – 2991 records identified through database searching and 121 additional records identified in reviews. After the removal of duplicates 2987 results remained. Following screening of titles and abstracts, 127 were eligible for full-text analysis. After full-text analysis, 23 studies met the inclusion criteria and were analysed. These findings were grouped based on pathology, producing 6 subgroups. No studies assessing OCD or depression met the inclusion criteria. The studies focused

on cannabinoids for the treatment of schizophrenia and psychosis, TS, ADHD, anxiety and PTSD. For more detailed information, see Figure 1.

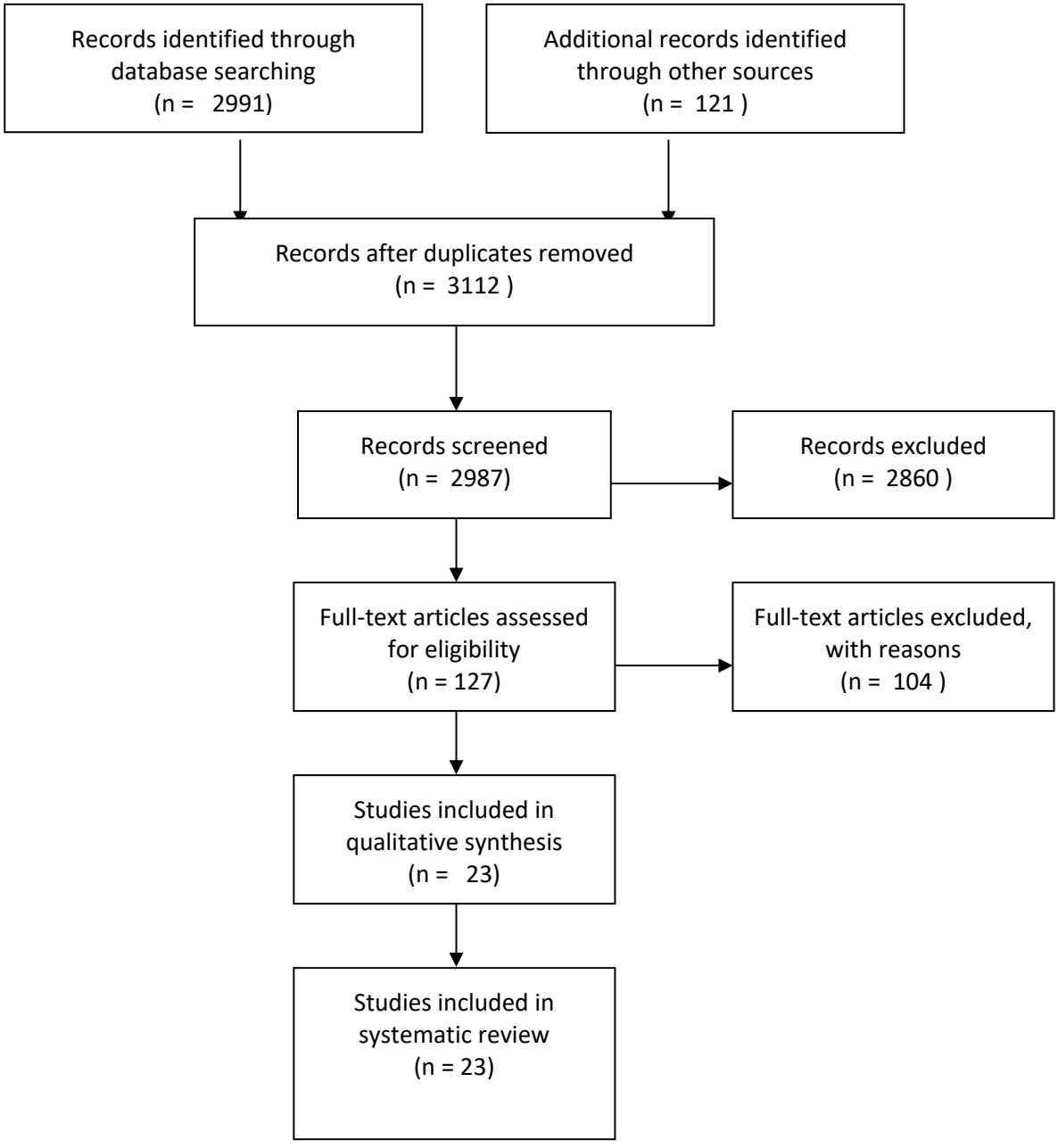

Fig 1. PRISMA flow diagram of the included studies

SCHIZOPHRENIA AND PSYCHOSIS

BACKGROUND

Schizophrenia is a neurodevelopmental disorder that tends to first present in early adulthood. It is characterised by a range of positive (hallucinations, delusional perceptions) and negative (apathy, social withdrawal) symptoms (APA, 2013). All currently licensed antipsychotic medicines work via dopamine receptor antagonism and can be associated with poor tolerability due to extrapyramidal and metabolic side effects (Tandon, 2011).

There is evidence that the eCBS is involved in the pathophysiology of schizophrenia. Schizophrenia patients show increased levels of endogenous cannabinoids in cerebrospinal fluid (Leweke et al., 1999; Giuffrida et al., 2004). The acute use of THC can cause a transient psychotic state in healthy participants and an exacerbation in core psychotic and cognitive deficits in schizophrenia (D'Souza *et al.*, 2004; Pierre, Gandal and Son, 2016). In addition, epidemiological studies indicate that cannabis use lowers the age of onset of illness and increases the risk of developing schizophrenia. In schizophrenia, cannabis use is related to higher rates of relapse, increased severity of symptoms, and an increased loss of grey matter volume (Bossong and Niesink, 2010).

The eCBS is also a promising therapeutic target. Several case reports have suggested an antipsychotic role of CBD, both as a monotherapy and as an adjunctive treatment to standard treatment (Makiol & Kluge, 2019; Zuardi et al., 1995, 2009). However, there is conflicting evidence (Schipper et al., 2018; Zuardi et al., 2006). The exact mechanism of CBD's antipsychotic effect is unclear. Two leading theories suggest that either CBD exerts an antipsychotic effect through (a) partial agonism of D2 receptors, similar to the atypical antipsychotic aripiprazole (Seeman, 2016); and, or (b) enhancing endocannabinoid signalling by inhibiting the reuptake of anandamide and reducing endocannabinoid degradation, thus allowing the stabilisation of dopamine neurotransmission (Gururajan and Malone, 2016; Pisanti *et al.*, 2017). Due to the limited nature of case reports, including lack of placebo-control and publication bias, the conclusions we can make from this evidence are restricted.

RESULTS

In total, seven clinical trials were identified as fulfulling the inclusion criteria for schizophrenia and psychosis. Every study used cannabidiol (CBD) as an intervention (see table 1).

Three studies investigated whether CBD modulates THC or ketamine-induced psychotic symptoms in healthy participants. Hallak et al., (2011) pretreated 10 healthy participants with 600mg CBD or placebo and then intravenously administered ketamine. Their results showed that CBD did not reduce ketamine-induced psychosis or depersonalisation. Bhattachrayya et al., (2010) also investigated CBD's effect on THC-induced psychotic symptoms in 6 healthy participants. They showed that pretreatment with CBD prevented acute induction of psychosis. Englund et al., (2013) also assessed the attenuating effects of CBD on THC-induced psychosis in 48 healthy participants. They were pre-treated with a single dose of 600mg of CBD or placebo and assessed using a variety of scales for psychotic symptoms, paranoia and memory. They demonstrated that CBD reduced THC-induced paranoia, memory impairment and positive psychotic symptoms. Overall, these studies provide evidence to suggest that CBD pretreatment can block the psychotogenic effects of THC but not ketamine.

Three studies investigated the effects of CBD in schizophrenia-associated symptoms including psychosis. In a randomised, double-blind controlled trial, Leweke et al., (2012) compared the effects of a four week trial of oral CBD to amisulpride in 39 inpatients with acute schizophrenia. They demonstrated that CBD was as effective as amisulpride in improvement of symptomatology and had a superior side-effect profile. These findings were in line with McGuire et al., (2018) who tested oral CBD for 6 weeks. They found that oral CBD significantly improved

psychotic symptoms compared to baseline, was well tolerated and had a similar side effect profile to placebo. However, these findings were not replicated by Boggs et al., (2018), who assessed the efficacy of adjunctive CBD compared to placebo in 36 patients who were already stable on antipsychotics. They found no significant difference between placebo and CBD despite both improving psychotic symptoms. This difference may be explained by the different uses of multiple antipsychotics between the placebo (38.9%) and CBD groups (11%). In addition, variations in dose, duration of treatment, concurrent comorbidities and medication make it difficult to compare findings.

One study was identified which investigated the effect of cannabidiol treatment on response inhibition in patients with psychosis. In a double-blind, placebo-controlled crossover study, Hallak et al., (2010) assessed performance of the Stroop Colour Word Test (SCWT) in 28 patients with acute schizophrenia, treated with a single-dose of placebo, 300mg or 600mg CBD. SCWT tests executive function, a key brain function often disrupted in schizophrenia. They showed that a single dose of CBD did not improve SCWT performance compared to placebo and had no effect on psychotic symptoms. There was also a sedative effect of 600mg of CBD. This suggested that single doses of CBD do not have a beneficial effect on cognitive performance in schizophrenia.

Overall, the results described above suggest that CBD may have potential as an antipsychotic in drug-induced psychosis and psychotic symptoms in schizophrenia.

TABLE 1a. RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN SCHIZOPHRENIA AND PSYCHOSIS										
Reference	Study Type	Intervention / Controls	Drug	Dose	Duration	Control	Outcome	Diagnosis	Result	Level of Evidence
(Bhattacharyya *et al.*, 2010)	Controlled, randomised, crossover trial	6 / 6	CBD	5mg	Single dose	Placebo	PANSS	THC-induced (1.25mg I) psychosis in healthy participants	CBD pre-treatment prevented THC-induced psychosis	2b
(Boggs *et al.*, 2018)	Randomised, placebo-controlled, parallel group	36	CBD	600mg	6 weeks	Placebo	PANSS MCCB HVLT WAIS	Stable antipsychotic-treated schizophrenia	CBD augmentation improved psychotic symptoms, but this was not significant compared to placebo. Only the placebo group had improved cognitive performance. CBD was well tolerated with no significant adverse effects.	2b
(Englund *et al.*, 2013)	Between-participants, controlled	22 / 26	CBD	600mg	Single dose	Placebo	PANSS SSPS HVLT-R	Healthy participants with THC-induced (1.25mg IV) Psychosis	CBD reduced THC-induced paranoia, memory impairment and improved clinically significant positive symptoms	1b

(Hallak *et al.*, 2010)	Double-blind, placebo-controlled study	28	CBD	300mg or 600mg	Single Dose	Placebo	SCWT BPRS PANSS	Schizophrenia	CBD 300mg and placebo improved SCWT performance but there was no statistically significant difference between the group. Each treatment had no effect on psychotic symptoms. Sedative effect with 600mg dose.	2b
(Hallak *et al.*, 2011)	Controlled, crossover trial	10 / 10	CBD	600mg	Single dose	Placebo	CADSS BPRS	Healthy participants with Ketamine-Induced (0.26 mg/kg) Psychosis	CBD increased ketamine-induced psychomotor activation and attenuated depersonalisation (non-significant)	2b
(Leweke *et al.*, 2012)	Double-blind, monocentre, parallel-group, RCT	20 / 19	CBD	200-800mg/d	4 weeks	Amisulpride	BPRS PANSS	Acute Schizophrenia	CBD as effective as amisulpride in terms of improvement of symptomatology and had superior side-effect profile. CBD significantly increased serum anandamide levels.	1b

(McGuire *et al.*, 2018)	Multicentre, double-blind, randomized, placebo-controlled, parallel-group trial	43 / 45	CBD	1000mg	6 weeks	Placebo	PANSS CGI-S BACS GAF	Antipsychotic-treated schizophrenia patients	CBD group had significant reduction in positive psychotic symptoms and CBD-treated patients were more likely rated as improved (CGI). CBD group had non-significant improvement in cognitive and general illness symptoms. CBD was well tolerated with side effects similar to placebo.	1b

BACS – brief assessment of cognition in schizophrenia; BPRS – brief psychiatric rating scale; CAARMS – comprehensive assessment of at risk mental states; CADSS – clinical administered dissociative states scale; CBD – cannabidiol; CGI – clinical global impression-severity; FAB – frontal assessment battery; GAF – global assessment of functioning; HVLT-R – Hopkins verbal learning test-revised; MCCB – matrics consensus cognitive battery; MMSE – mini-mental state examination; PANSS – positive and negative syndrome scale; PPQ – Parkinson Psychosis Questionnaire; RCT – randomised controlled trial; SCWT – stroop colour word test; SSPS – state social paranoid scale; STAI – state-trait anxiety inventory; THC – tetrahydrocannabinol; UPDRIS – unified parkinson's disease rating scale; WAIS – Weschler adult intelligence scale

TABLE 1b. RISK OF BIAS ASSESSMENT FOR RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN SCHIZOPHRENIA AND PSYCHOSIS

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias
(Bhattacharyya *et al.*, 2010)	?	+	+	+	?	?	?
(Boggs *et al.*, 2018)	?	?	+	?	+	+	?

(Englund *et al.*, 2013)	?	+	+	?	?	+	?
(Hallak *et al.*, 2010)	-	+	+	?	+	+	?
(Hallak *et al.*, 2011)	?	+	+	+	+	+	?
(Leweke *et al.*, 2012)	+	+	+	+	?	+	?
(McGuire *et al.*, 2018)	+	+	+	+	+	+	+

Green (+) = low risk; yellow (?) = unclear risk; red (-) = high risk

DEPRESSION

BACKGROUND

Depression is the most common psychiatric disorder, affecting approximately 20% of the population. It is characterised by low mood and anhedonia (APA, 2013). Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacological treatment.

The eCBS is involved in mood regulation (Campolongo and Trezza, 2012) and bipolar disorder . Common acute effects of cannabis use include mood elevation and euphoria (Hall and Degenhardt, 2009). These effects are induced through activation of CB1 receptors, suggesting a putative role for substances that increase eCB levels in the treatment of mood disorders. Preclinical studies have reported depressive symptoms in CB1-knockout mice and antidepressant effects of CBD (Martin *et al.*, 2002; Linge *et al.*, 2016). Furthermore, antagonism at CB1 receptors with rimonabant caused severe depression and suicidal ideation in humans (Christensen *et al.*, 2007). In lieu of these findings, a review is urgently needed to assess the therapeutic role of cannabis in depression.

RESULTS

Overall, no studies were identified which met the inclusion criteria for depression.

BIPOLAR AFFECTIVE DISORDER (BPAD)

BACKGROUND

BPAD is a mental disorder characterised by periods of depression and abnormally elevated mood (APA, 2013). Cases of mania or hypomania involve treatment with atypical dopamine antagonists and mood stabilisers. Cannabis use is much more common in individuals with BPAD compared to the general population. Over and above the antidepressant and antipsychotic effects that are of potential use in BPAD, cannabinoids may have antimanic effects. There have been anecdotal reports which suggest that cannabis can be used for self-medication in alleviating depression and mania (Gruber et al., 1996, Grinspoon and Bakalar, 1998). However, there is a lack of clinical systematic reviews assessing cannabinoids in the treatment of BPAD.

RESULTS

Overall, no studies were identified which met the inclusion criteria for BPAD.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

BACKGROUND

ADHD is a disorder characterised by inattention, hyperactivity and impulsivity, pervasive in multiple settings and often presenting in childhood (Asherson *et al.*, 2016). Pharmacological management involves pro-dopaminergic drugs, such as methylphenidate.

People with ADHD often have comorbid substance use and it has been hypothesised that increased cannabis use may be related to self-medication for hyperactivity (Loflin *et al.*, 2014). Recent evidence has suggested that the eCBS may be involved in the pathophysiology of ADHD. Patients with ADHD have impaired anandamide metabolism compared to healthy controls (Centonze *et al.*, 2009). In addition, genetic studies have found a correlation between the cannabinoid receptor gene (CNR1) and development of ADHD (Lu *et al.*, 2008). In a large case series of 30 treatment-resistant adults with ADHD, it was found that medicinal cannabis improved a variety of ADHD-related symptomatology including poor concentration, sleep disturbance and impulsivity (Milz and Grotenhermen, 2015). Other case reports have also supported these findings (Strohbeck-kuehner et al., 2008). Overall, there is evidence to support assessing cannabinoids as an alternative treatment option in ADHD.

RESULTS

Only one randomised controlled clinical trial has assessed the effects of cannabinoids in the treatment of ADHD (see table 2). Cooper et al., (2017) compared the effects of Sativex (THC and CBD mucosal spray) to placebo in 15 participants with ADHD. Sativex was associated with a significant improvement in inhibition and hyperactivity/impulsivity. There was one serious (muscle spasms) and three mild adverse effects in the Sativex group compared to one serious adverse effect (cardiovascular problems) in the placebo group. Additionally, patients with comorbid psychiatric disorders were excluded, so the results may not be representative of an ADHD population as they have several comorbidities. There was also a wide variation in dose (1 – 13 sprays per day).

Overall, this study does not provide definitive evidence to support the use of cannabis in ADHD. However, there is still potential for cannabinoids in the treatment of ADHD and more studies with larger sample over longer periods of time are required.

TABLE 2a. RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER										
Reference	Study Type	Intervention / Controls	Drug	Dose	Duration	Control	Outcome	Diagnosis	Result	Level of Evidence
(Cooper *et al.*, 2017)	Double-blind, placebo controlled RCT	15 / 15	Sativex (THC+CBD)	4.5 sprays/d (12.15mg THC and 11.25mg CBD)	6 weeks	Placebo	QbTest CAARS WRAADS SART CNS-LS ALS-SF WFIRS-S	ADHD	Sativex reduced hyperactivity, impulsivity and cognitive measure on inhibition. No difference placebo and Sativex group in emotional lability, cognitive performance, activity level or inattention	1b

ADHD – attention-deficit hyperactivity disorder; ALS-SF - Affective lability scale-short form; CAARS – Conners Adult ADHD Rating Scale; CBD – cannabidiol; CNS-LS – centre for neurologic study lability scale; QbTest – Quantitative Behavioural Test ; SART – sustained attention to response task; THC – delta-9-tetrahydrocannabinol; WFIRS-S – Weiss functional impairment rating scale self-report; WRAADS – Wender-Reimherr Adult Attention Deficit Disorder Scale

TABLE 2b. RISK OF BIAS ASSESSMENT FOR RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER							
Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias
(Cooper *et al.*, 2017)	+	+	+	+	?	+	?

Green (+) = low risk; yellow (?) = unclear risk; red (-) = high risk

ANXIETY DISORDERS

BACKGROUND

Anxiety disorders are a group of mental disorders characterised by significant feelings of anxiety and fear leading to a disruption in mental wellbeing. Generalised anxiety disorder (GAD) is characterised by general irritability, anxiety and chronic anxiety. Panic disorder (PD) features brief spells of overwhelming anxiety accompanied with somatic symptoms. Social anxiety disorder (SAD) features extreme anxiety in social situations and secondary avoidance. Current pharmacological management for anxiety disorders includes antidepressants, beta-blockers and benzodiazepines.

There is a high comorbidity of cannabis use in those with anxiety disorders (Kedzior and Laeber, 2014), perhaps suggesting a self-therapeutic strategy as relaxation and reduction of anxiety are common uses for cannabis. However, chronic consumption of cannabis has been suggested to actually exacerbate anxiety and reduce the efficacy of anxiolytic agents (Mammen *et al.*, 2018). There also seems to be a biphasic effect of CB1 receptor agonism as a function of dose. Many users report an optimal dose of cannabis results in euphoria and relaxation whereas high doses can induce dysphoria and panic (Thomas, 1996; Groce, 2018). These findings have been demonstrated by several animal preclinical models of anxiety (Fattore, 2015). Conversely, CBD does not exert anxiogenic effects and has been shown to reduce anxiety-related behaviour in preclinical models (Fattore, 2015). This suggests that CBD may be useful in treatment of anxiety.

RESULTS

Twelve studies were identified which investigated the therapeutic potential of cannabinoids in experimentally-induced anxiety and anxiety disorders (see table 3).

Three studies showed that CBD reduced THC-induced anxiety (Karniol *et al.*, 1974; Zuardi *et al.*, 1982; Crippa *et al.*, 2004). In a double-blind RCT, Karniol et al., (1974) induced anxiety with 15, 30 or 60mg of intravenous THC in 40 healthy participants and then treated them with 15, 30 or 60mg oral CBD and found that CBD reduced THC-induced anxiety and pulse rate. Thus providing the first evidence that CBD attenuates THC-induced anxiety. Two similar studies also found that a single dose of CBD (400mg and 300mg respectively) decreased IV THC-induced anxiety (Zuardi *et al.*, 1982; Crippa *et al.*, 2004). Overall, these studies suggest that oral CBD can ameliorate THC-induced anxiety.

Four studies assessed the anxiolytic effect of CBD in healthy participants with either the Simulated Public Speaking Test- (Zuardi *et al.*, 1993, 2017; Linares *et al.*, 2019) or fearful face-induced anxiety (Fusar-Poli *et al.*, 2010). In a double-blind RCT, Zuardi et al., (1993) found that 300mg CBD pre-treatment was comparable to Ipsapirone (5mg) in reducing anxiety in 40 healthy participants during a SPST. These findings were confirmed by the same group in that 300mg of CBD reduced anxiety (Zuardi *et al.*, 2017). However, in a bell-shaped curve response 100mg and 900mg of CBD had no effect on anxiety compared to placebo. In line with these findings, Linares et al., (2010) showed that a single dose of CBD 300 mg, but not 150 or 600 mg, led to a decrease in SPST-induced anxiety. This inverted U-response feature of CBD attenuating anxiety is also mirrored in preclinical studies (Guimarães *et al.*, 1990). The SPST is proposed to model SAD, as the fear of public speaking and somatic symptoms associated with it are core aspects of SAD. In a series of neuroimaging studies using fearful face stimuli, functional magnetic resonance imaging (fMRI) was used to investigate the neural correlates of the anxiolytic effects of CBD in 15 healthy participants. They found that 600mg of oral CBD reduced stimuli-increased skin conductance and attenuated responses in the

anterior and posterior cingulate and amygdala (Fusar-Poli *et al.*, 2010). Overall, the evidence provided shows that certain doses of CBD can attenuate induced anxiety in healthy participants.

Two double-blind RCTs assessed the effects of CBD in attenuated SPST-induced anxiety in treatment naïve SAD patients. Bergamaschi et al., (2011) showed that a single oral dose of 600mg CBD significantly attenuated anxiety and palpitations compared to placebo. Similarly, Crippa et al., (2011) employed fMRI in 10 treatment-naïve patients with social anxiety who were given 400 mg of oral CBD or placebo in a double-blinded crossover manner. Relative to placebo, 400 mg of CBD was associated with significantly decreased subjective anxiety, with blood flow being modulated in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and the right posterior cingulate gyrus. This suggests that CBD's effects may occur via interaction with the limbic and paralimbic brain areas. Overall, the evidence from RCTs suggests that CBD may be a useful therapeutic option in acute phases of social anxiety disorder.

Three studies assessed the effects of nabilone (a synthetic cannabinoid) in anxiety disorder. Two studies showed that nabilone reduced anxiety (Fabre and McLendon, 1981; Ilaria et al., 1981) whereas another found that nabilone did not significantly affect anxiety or related somatic symptoms (Glass *et al.*, 1980). This conflicting evidence is likely due to variation in duration (single dose compared to 28 days). Overall, there is insufficient evidence to infer a therapeutic role of nabilone in anxiety disorders.

TABLE 3a. RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN ANXIETY DISORDERS

Reference	Study Type	Intervention / Controls	Drug	Dose	Duration	Control	Outcome	Diagnosis	Result	Level of Evidence
(Bergamaschi *et al.*, 2011)	Double-blind RCT	12 / 12	CBD	600mg	Single dose	Placebo	VAMS SSPS-N BP HR SC BSPS	Treatment-naïve SAD (24) and Healthy participants (12)	In patients with SAD, pre-treatment with CBD resulted in significantly reduced anxiety, cognitive impairment and somatic symptoms when compared to placebo. No significant differences were found between SAD patients treated with CBD and healthy	2b

									controls, unlike what happened with SAD patients taking placebo.	
(Crippa *et al.*, 2011)	Double-blind, crossover RCT	10	CBD	400mg	Single dose	Placebo	VAMS rCBF using SPECT BSPS	Treatment-naïve Generalised SAD	Significant reduction of subjective anxiety in CBD group associated with reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and increased ECD uptake in the right posterior cingulate gyrus. No adverse effects	2b
(De Souza Crippa *et al.*, 2004)	Randomised, double-blind, placebo-controlled crossover	10	CBD	400mg	Single dose	Placebo	VAMS	Healthy participants with THC-induced (2.5 and 5mg IV) anxiety	CBD decreased VAS factor anxiety score elevation induced by THC	2b
(Fabre and McLendon, 1981)	Double-blind, placebo-controlled trial	20	Nabilone	3mg	28 days	Placebo	HRSA Patient's Global Evaluation Patient-rated Evaluations	Anxiety disorder	Improve in anxiety. Adverse effects of dry mouth, dry eyes and drowsiness	2b

(Fusar-Poli *et al.*, 2010)	Double-blind, randomised, placebo-controlled trial	15	CBD	600mg	Single dose	Placebo	SC	Healthy participants during fearful face task	Decreased skin conductance fluctuation in task with fearful face	2b
(Glass *et al.*, 1980)	Single-blind, Latin-square	8	Nabilone	1 or 2 OR 4 or 5mg	Single Dose	Placebo	HR BP POMS	Anxious Disorder	2/4 participants experienced an antianxiety effect from low dose nabilone. There were no other effects on anxiety, blood pressure or heart rate	2b
(Ilaria, Thornby and Fann, 1981)	Single-blind, placebo-controlled crossover trial	11	Nabilone	Up to 5mg/d	N / A	Placebo	Global Improvement Scale HRSA	Anxious neurotic patients	Improvement in anxiety	2b
(Karniol *et al.*, 1974)	Double-blind RCT	40	CBD	15, 30 and 60mg	Single dose	Placebo	Anxiety HR	Healthy participants with THC-induced (15, 30 or 60mg) anxiety	CBD reduced THC-induced increase anxiety and pulse rate but had no effect when given alone	2b
(Linares *et al.*, 2019)	Double-blind RCT	42 / 15	CBD	150, 300 and 600mg	Single dose	Placebo	VAMS BP HR	Healthy participants with SPST-induced anxiety	Compared to placebo, pre-treatment with 300 mg of CBD significantly reduced anxiety during the	1b

									speech. No significant differences in VAMS scores were observed between groups receiving CBD 150 mg, 600 mg and placebo.	
(Zuardi *et al.*, 1982)	Double-blind RCT	8	CBD	1mg/kg	Single dose	Placebo Diazepam 10mg	STAI VAMS BP HR	Healthy participants with THC-induced (0.5mg/kg IV) anxiety	CBD blocks THC-induced increase in STAI, VAMS and BP and reduced anxiety at baseline	2b
(Zuardi *et al.*, 1993)	Double-blind RCT	10	CBD	300mg	Single dose	Diazepam 10mg Ipsapirone 5mg Placebo	VAMS STAI HR BP SC	Healthy participants with SPST-induced anxiety	CBD, diazepam and Ipsapirone reduced SPS-induced anxiety on the VAS and STAI scale. CBD had no adverse effects.	2b
(Zuardi *et al.*, 2017)	Double-blind, placebo-controlled trial	6	CBD	100, 300 and 900mg	Single dose	Clonazepam 1mg Placebo	TPSRS	Healthy volunteers with TPSRS-induced anxiety	Compared to placebo 300 mg of CBD significantly reduced anxiety symptoms. No significant differences were observed between groups receiving CBD 100 mg, 900 mg and placebo.	2b

BP – blood pressure; BSPS – brief social phobia scale; CADSS – clinician-administered dissociative states scale; CBD – cannabidiol; HR – heart rate; HRSA – Hamilton rating scale for anxiety; POMS – profile of mood states; rCBF – regional cerebral blood flow; RCT – randomised controlled trial; SPSS-N – negative self-statement scale; SPST –

simulated public speaking test; SAD – social anxiety disorder; SC – skin conductance; SPECT – single-photon emission computerised tomography; STAI – state-trait anxiety inventory; THC – tetrahydrocannabinol; TPSRS – test of public speaking in a real situation; VAMS – visual analogue mood scale;

TABLE 3b. RISK OF BIAS ASSESSMENT FOR RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN ANXIETY DISORDERS

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias
(Bergamaschi *et al.*, 2011)	?	?	+	+	+	+	?
(Crippa *et al.*, 2011)	-	?	?	?	+	+	?
(De Souza *et al.*, 2004)	?	?	+	?	+	+	?
(Fabre and McLendon, 1981)	-	?	+	?	+	+	?
(Fusar-Poli *et al.*, 2010)	-	+	+	+	?	?	?
(Glass *et al.*, 1980)	-	?	-	?	+	-	-
(Ilaria, Thornby and Fann, 1981)	-	-	-	-	?	?	?
(Karniol *et al.*, 1974)	-	+	+	?	+	+	?
(Linares *et al.*, 2019)	?	+	+	?	+	+	+
(Zuardi *et al.*, 1982)	-	?	+	?	+	+	?
(Zuardi *et al.*, 1993)	?	+	+	+	+	+	?
(Zuardi *et al.*, 2017)	?	+	+	+	+	+	?

Green (+) = low risk; yellow (?) = unclear risk; red (-) = high risk

POST-TRAUMATIC STRESS DISORDER (PTSD)

BACKGROUND

PTSD is characterised by intrusion memories such as nightmares and flashbacks, avoidance of trauma-related stimuli and hyperarousal (APA, 2013). There is a growing body of evidence suggesting that the eCBS plays a key role in PTSD pathophysiology. Importantly, the eCBS is involved in emotional memory, determining the value or fear-evoking stimuli and stress resilience (Lutz *et al.*, 2015). Cannabinoid receptor availability has been linked to attention bias to threat, a key feature in PTSD (Glass et al., 1997; Nutt and Malizia, 2004; Stevens *et al.*, 2017).

There is evidence that people with PTSD use cannabinoids for symptomatic relief with varying success (Hindocha et al., 2020). Case reports suggest that nabilone, THC and CBD greatly reduce PTSD-associated symptoms, particularly sleep disturbance and anxiety (Fraser, 2009; Cameron, Watson and Robinson, 2014; Roitman *et al.*, 2014; Shannon and Opila-Lehman, 2016; Elms *et al.*, 2019). Overall, these studies suggest that nabilone, THC and CBD may be useful in the treatment of PTSD, particularly sleep disturbances and nightmares.

RESULTS

Only one randomised, controlled trial assessed the therapeutic effects of cannabinoids in PTSD (see table 4). In a double-blind RCT, Jetly et al., (2015) investigated the efficacy of oral nabilone capsules in PTSD-associated nightmares in Canadian male military personnel with persistent nightmares. 10 participants were given either 500 micrograms of nabilone (titrated upwards to 3mg or maximal tolerated dose) or placebo for a period of 7 weeks. After a two-week washout period, the drugs were switched over. They demonstrated that nabilone improves sleep quality, general wellbeing and reduced nightmares as measured by a wellbeing questionnaire and clinically administered PTSD scales. Further RCTs are required to strengthen these findings. However, there is promising evidence that nabilone is beneficial in PTSD-associated sleep disturbance.

TABLE 4a. RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN POST-TRAUMATIC STRESS DISORDERS

Reference	Study Type	Intervention / Controls	Drug	Dose	Duration	Control	Outcome	Diagnosis	Result	Level of Evidence
(Jetly *et al.*, 2015)	Pilot, Double-blind crossover RCT	10	Nabilone	500mcg – 3mg	16 weeks	Placebo	CAPS WBQ CGI-C	PTSD	Significant improvement in nightmare severity, wellbeing and disease severity but no	2b

									improvement in sleep quality. Nabilone was well tolerated and no significant difference in adverse effects compared to placebo.	

CAPS – clinical administered post-traumatic stress disorder scale; CGI-C – clinical global impression of change; PTSD – posttraumatic stress disorder; RCT – randomised controlled trial; WBQ – wellbeing questionnaire

TABLE 4b. RISK OF BIAS ASSESSMENT FOR RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN POST-TRAUMATIC STRESS DISORDERS							
Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias
(Jetly *et al.*, 2015)	+	+	+	+	+	+	?

Green = low risk; yellow = unclear risk; red = high risk

OBSESSIVE-COMPULSIVE SPECTRUM DISORDERS (OCD)

BACKGROUND

OCD is a condition characterised by recurrent, distressing thoughts, as well as a strong urge to perform repetitive stereotyped behaviours to relieve distress caused by obsessions. OCD is associated with dysfunction in the cortico-striato-thalamic circuit, which has a high density of CB1 receptors, including in the basal ganglia and prefrontal cortex (Glass et al., 1997; Fitzgerald *et al.*, 2011). There is evidence from animal models of OCD using the marble-burying paradigm that cannabinoids including direct CB1 receptor agonists and cannabidiol decrease the number of buried marbles (Casarotto *et al.*, 2010; Umathe, Manna and Jain, 2011; Deiana *et al.*, 2012). Accordingly, recent clinical studies have shown that THC elicits therapeutic effects in OCD and trichotillomania, an impulse-control disorder characterized by compulsive hair-pulling (Schindler *et al.*, 2008; Grant *et al.*, 2011). Overall, the evidence indicates that the eCBS is an important target for new therapeutic approaches in OCD.

RESULTS

No studies were identified which met our inclusion criteria for OCD.

TOURETTE'S SYNDROME

BACKGROUND

Tourette's is a neurodevelopmental disorder of childhood-onset characterised by tics. Tics are sudden, repetitive and involuntary movements. First-line pharmacological management for Tourette's is dopamine antagonists. There is often reluctance amongst clinicians to prescribe dopamine antagonists for Tourette's, particularly in children, due to their deleterious side effect profile (Huys *et al.*, 2012).

A leading hypothesis is that Tourette's is caused by disinhibition of the cortico-striato-thalamo-cortical system. This is supported by the efficacy of first-line pharmacological treatment of dopamine receptor antagonists in tic suppression (Pringsheim *et al.*, 2019). CB1 receptors are found in high density in the basal ganglia, suggesting that the eCBS is involved in movement control. THC has also been shown to modulate dopaminergic transmission (Bloomfield *et al.*, 2016). There is evidence from case reports describing the beneficial effects of cannabinoid-based medicine in the treatment of tics, particularly in reducing tic severity and premonitory urge (Sandyk and Awerbuch, 1988; Muller-Vahl *et al.*, 1999, 2002a; 2002b; Hasan *et al.*, 2010; Brunnauer *et al.*, 2011; Szejko *et al.*, 2019). In these studies, trials of THC, CBD and cannabis were all well tolerated with minimal side effects. However, due to the nature of case reports, no placebo was used and several of the studies performed no statistical analysis or objective measurement of tic severity, which limits the conclusions that can be made from these studies.

Overall, there is biological rationale for the role of cannabinoids in the treatment of Tourette's. The deleterious effects of pharmacological treatment for Tourette's also warrant exploration for a more tolerable and equally efficacious medicine. Preliminary reports suggest a role of THC and CBD in treatment-resistant Tourette's and a review of clinical trials assessing the efficacy of cannabinoids in Tourette's is warranted.

RESULTS

Only two randomised, double-blind, placebo-controlled trials have been done to assess the effects of cannabinoid-based medicine in Tourette's syndrome (see table 5). In a double-blind, parallel group RCT, 12 patients were treated with 5, 7.5 or 10mg of oral THC or placebo for two days (Müller-Vahl *et al.*, 2002). This was followed by a 4-week washout and then switched over to either placebo or THC. THC led to a significant dose-dependent improvement in tics. Five patients had mild adverse effects transiently following THC including light-headedness and poor concentration. In clinical practice, doses of THC are gradually uptitrated which would likely reduce the incidence of adverse effects. In a similar design, the same group investigated the efficacy of oral THC over 6 weeks in 24 patients with Tourette's (Müller-Vahl *et al.*, 2003). They increased the dose by 2.5mg every 4 days beginning with 2.5mg until a maximum of 10mg/day was reached or adverse events occurred. Compared to placebo, oral THC led to an improvement in tic severity. One patient in the THC dropped out due to adverse effects (anxiety and restlessness). There were no other sustained adverse effects. Overall, the results of these clinical trials suggest that oral THC may be useful as a treatment for Tourette's. However, these results are yet to be replicated by other groups, therefore there is an urgent need for larger clinical trials from other groups.

TABLE 5a. RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN TOURETTE'S SYNDROME

Reference	Study Type	Intervention / Controls	Drug	Dose	Duration	Control	Primary Outcome	Diagnosis	Result	Level of Evidence

(Müller-Vahl *et al.*, 2002)	Double-blind RCT	12	THC	5, 7.5 or 10mg/d	2 days	Placebo	TSSL TSGS SCL-90-R	TS	THC reduced tics and led to improvement in OCB	1b
(Müller-Vahl *et al.*, 2003)	Double-blind, parallel group RCT	24	THC	2.5-10mg/d	6 weeks	Placebo	CGI STSS YGTSS Rush videotape-based rating scale	TS	THC reduced tics and led to a global improvement	2b

CGI – clinical global impression; OCB – obsessive-compulsive behaviour; RCT – randomised controlled trial; SCL-90-R – symptom checklist 90-R; STSS – Shapiro Tourette's syndrome severity scale; THC – delta-9-tetrahydrocannabinol; TS – Tourette's syndrome; TSGS – Tourette's Syndrome Global Scale; TSSL – Tourette's syndrome symptom list; YGTSS – Yale Global Tic Severity Scale

TABLE 5b. RISK OF BIAS ASSESSMENT FOR RANDOMISED CONTROLLED TRIALS OF CANNABINOIDS IN TOURETTE'S SYNDROME

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias
(Müller-Vahl *et al.*, 2002)	?	+	+	+	+	+	?
(Müller-Vahl et al., 2003)	?	+	+	+	-	?	?

Green (+) = low risk; yellow (?) = unclear risk; red (-) = high risk

DISCUSSION

The aim of this study was to evaluate the therapeutic effects of cannabis in the treatment of neuropsychiatric populations. Efficacy was shown for CBD in the treatment of THC and ketamine-induced psychosis, acute psychosis, stable schizophrenia and those with a clinically high risk of developing psychosis. Overall, this suggests that CBD has a putative role in the treatment of schizophrenia and acute psychosis. A handful of studies suggest a benefit of CBD in reducing anxiety, particularly CBD pre-treatment in performance-related or THC-induced anxiety. However, most studies are on healthy participants with anxiety induced using public speaking tests and THC. In PTSD, the data is sparse but promising and suggests that nabilone may be beneficial in PTSD-associated sleep disturbance. There were no RCTs assessing the role of cannabis in the treatment of OCD, bipolar disorder or depression as a primary outcome. Two trials have found efficacy of THC in reduction of tics and a global improvement of functioning in patients with Tourette's. However, these studies are from the same group and more trials with different TS populations are required to draw firm conclusions on the efficacy of THC in TS. With regards to CBD administration, only mild adverse effects were reported, including sedation. Most studies showed adverse effects were comparable to placebo and more tolerable than standard treatment. Overall, these findings are in keeping with other systematic reviews assessing the effects of cannabinoids in psychiatric disorders (Crippa et al., 2010; Hindocha *et al.*, 2020; Sarris *et al.*, 2020).

LIMITATIONS

Only studies in English were considered and only PubMed was searched which may exclude relevant studies and thus affect any conclusions drawn. Secondly, there was a large degree of heterogeneity across studies in terms of dose, duration of each intervention, study population, concurrent psychotropic medication, stage of disease and comorbidities; thus, limiting the comparisons that could be made across studies. Most of the RCTs also had a small sample size. Lastly, most studies did not report biological measures of cannabinoid levels which would have implications in terms of defining therapeutic efficacy.

RECOMMENDATIONS FOR FUTURE RESEARCH

The findings of the above studies need to be validated by larger, randomised, double-blinded and placebo-controlled studies. Future studies should use standardised dose, formulation, duration of the intervention and focus on controlling key features of the study population – diagnostic criteria, concurrent and previously trialled medications. They should also use biological measures of drug levels to confirm dosage in participants and enable comparisons to be made across studies. Future studies should also compare standard treatment with an alternative cannabinoid option. Larger sample sizes as well as standardised inclusion/exclusion criteria for participants will help to reduce heterogeneity and compare findings across studies. In this way, one will also be able to address conflicting evidence. Future studies should also focus on longer duration of the intervention and assess safety and tolerability of cannabinoids, as well as any potential addictive and abusive profile over long-term use. Lastly, future studies should aim to focus on risk versus benefit analysis and determine an optimal dose to limit side effects and reduce abuse liability.

CONCLUSION

At present, the use of cannabinoids in clinical practice cannot be recommended with confidence due to the paucity and limitations of existing evidence. In order to approve the use of cannabinoids for the treatment of neuropsychiatric disorders, more well-designed and highly powered controlled RCTs are necessary. There is promising evidence for the role of CBD in the treatment of schizophrenia, psychosis and anxiety. However, there is an urgent need for more high-level clinical evidence before it can be recommended as a therapeutic approach. There is also promise for nabilone in PTSD-associated sleep disturbance and THC in Tourette's syndrome. Future

studies should focus on standardised methodology and longitudinal assessment to strengthen understanding of the therapeutic role of cannabis in the psychiatric population.

BIBLIOGRAPHY

American Psychiatric Association (2013) 'DSM-5 Diagnostic Classification', in *Diagnostic and Statistical Manual of Mental Disorders*. doi: 10.1176/appi.books.9780890425596.x00diagnosticclassification.

Asherson, P. *et al.* (2016) 'Adult attention-deficit hyperactivity disorder: Key conceptual issues', *The Lancet Psychiatry*. doi: 10.1016/S2215-0366(16)30032-3.

Bergamaschi, M. M. *et al.* (2011) 'Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-nave social phobia patients', *Neuropsychopharmacology*. doi: 10.1038/npp.2011.6.

Bhattacharyya, S. *et al.* (2010) 'Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology', *Neuropsychopharmacology*. doi: 10.1038/npp.2009.184.

Bloch, M. H. *et al.* (2006) 'A systematic review: Antipsychotic augmentation with treatment refractory obsessive-compulsive disorder', *Molecular Psychiatry*. doi: 10.1038/sj.mp.4001823.

Bloomfield, M. A. P. *et al.* (2016) 'The effects of δ9-tetrahydrocannabinol on the dopamine system', *Nature*. doi: 10.1038/nature20153.

Boggs, D. L. *et al.* (2018) 'The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial', *Psychopharmacology*. doi: 10.1007/s00213-018-4885-9.

Bossong, M. G. and Niesink, R. J. M. (2010) 'Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia', *Progress in Neurobiology*. doi: 10.1016/j.pneurobio.2010.06.010.

Brunnauer, A. *et al.* (2011) 'Cannabinoids improve driving ability in a Tourette's patient', *Psychiatry Research*. doi: 10.1016/j.psychres.2011.05.033.

Cameron, C., Watson, D. and Robinson, J. (2014) 'Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: A retrospective evaluation', *Journal of Clinical Psychopharmacology*. doi: 10.1097/JCP.0000000000000180.

Campolongo, P. and Trezza, V. (2012) 'The endocannabinoid system: A key modulator of emotions and cognition', *Frontiers in Behavioral Neuroscience*. doi: 10.3389/fnbeh.2012.00073.

Casarotto, P. C. *et al.* (2010) 'Cannabidiol inhibitory effect on marble-burying behaviour: Involvement of CB1 receptors', *Behavioural Pharmacology*. doi: 10.1097/FBP.0b013e32833b33c5.

Centonze, D. *et al.* (2009) 'Altered anandamide degradation in attention-deficit/hyperactivity disorder', *Neurology*. doi: 10.1212/WNL.0b013e3181a2e8f6.

Christensen, R. *et al.* (2007) 'Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials', *Lancet*. doi: 10.1016/S0140-6736(07)61721-8.

Cooper, R. E. *et al.* (2017) 'Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial', *European Neuropsychopharmacology*. doi: 10.1016/j.euroneuro.2017.05.005.

Crippa, J. A. S. *et al.* (2011) 'Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report', *Journal of Psychopharmacology*. doi: 10.1177/0269881110379283.

Crippa, J. A. S., Zuardi, A. W. and Hallak, J. E. C. (2010) '[Therapeutical use of the cannabinoids in psychiatry].', *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*.

Curran, H. V. *et al.* (2016) 'Keep off the grass? Cannabis, cognition and addiction', *Nature Reviews Neuroscience*, pp. 293–306. doi: 10.1038/nrn.2016.28.

D'Souza, D. C. *et al.* (2004) 'The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis', *Neuropsychopharmacology*. doi: 10.1038/sj.npp.1300496.

Deiana, S. *et al.* (2012) '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 behav', *Psychopharmacology*. doi: 10.1007/s00213-011-2415-0.
Elms, L. *et al.* (2019) 'Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series', *Journal of Alternative and Complementary Medicine*. doi: 10.1089/acm.2018.0437.
Emsley, R. *et al.* (2013) 'The nature of relapse in schizophrenia', *BMC Psychiatry*. doi: 10.1186/1471-244X-13-50.
Englund, A. *et al.* (2013) 'Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment', *Journal of Psychopharmacology*. doi: 10.1177/0269881112460109.
FABRE, L. F. and McLENDON, D. (1981) 'The Efficacy and Safety of Nabilone (A Synthetic Cannabinoid) in the Treatment of Anxiety', *The Journal of Clinical Pharmacology*. doi: 10.1002/j.1552-4604.1981.tb02617.x.
Fattore, L. (2015) *Cannabinoids in Neurologic and Mental Disease*, *Cannabinoids in Neurologic and Mental Disease*. doi: 10.1016/C2013-0-00592-0.
Fitzgerald, K. D. *et al.* (2011) 'Developmental alterations of frontal-striatal-thalamic connectivity in obsessive-compulsive disorder', *Journal of the American Academy of Child and Adolescent Psychiatry*. doi: 10.1016/j.jaac.2011.06.011.
Fraser, G. A. (2009) 'The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD)', *CNS Neuroscience and Therapeutics*. doi: 10.1111/j.1755-5949.2008.00071.x.
Fusar-Poli, P. *et al.* (2010) 'Modulation of effective connectivity during emotional processing by Δ9-tetrahydrocannabinol and cannabidiol', *International Journal of Neuropsychopharmacology*. doi: 10.1017/S1461145709990617.
Glass, M., Faull, R. L. M. and Dragunow, M. (1997) 'Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study on the fetal, neonatal and adult human brain', *Neuroscience*, 77(2), pp. 299–318. doi: S0306452296004289 [pii].
Glass, R. M. *et al.* (1980) 'A single dose study of nabilone, a synthetic cannabinoid', *Psychopharmacology*. doi: 10.1007/BF00434401.
Grant, J. E. *et al.* (2011) 'Dronabinol, a cannabinoid agonist, reduces hair pulling in trichotillomania: A pilot study', *Psychopharmacology*. doi: 10.1007/s00213-011-2347-8.
Groce, E. (2018) 'The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research', *Journal of Medical Regulation*. doi: 10.30770/2572-1852-104.4.32.
Guimarães, F. S. *et al.* (1990) 'Antianxiety effect of cannabidiol in the elevated plus-maze', *Psychopharmacology*. doi: 10.1007/BF02244012.
Gururajan, A. and Malone, D. T. (2016) 'Does cannabidiol have a role in the treatment of schizophrenia?', *Schizophrenia Research*. doi: 10.1016/j.schres.2016.06.022.
Hall, W. and Degenhardt, L. (2009) 'Adverse health effects of non-medical cannabis use', *The Lancet*. doi: 10.1016/S0140-6736(09)61037-0.
Hallak, J. E. C. *et al.* (2010) 'Performance of schizophrenic patients in the Stroop Color Word Test and electrodermal responsiveness after acute administration of cannabidiol (CBD)', *Revista Brasileira de Psiquiatria*. doi: 10.1590/S1516-44462010000100011.
Hallak, J. E. C. *et al.* (2011) 'The interplay of cannabinoid and NMDA glutamate receptor systems in humans: Preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. doi: 10.1016/j.pnpbp.2010.11.002.
Hasan, A. *et al.* (2010) 'Oral Δ9-tetrahydrocannabinol improved refractory Gilles de la Tourette syndrome in an adolescent by increasing intracortical inhibition: A case report', *Journal of Clinical Psychopharmacology*. doi: 10.1097/JCP.0b013e3181d236ec.
Higgins, J. P. *et al.* (2019) 'Assessing risk of bias in a randomized trial', in *Cochrane Handbook for Systematic*

Reviews of Interventions. doi: 10.1002/9781119536604.ch8.
Hindocha, C. *et al.* (2015) 'Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users', *European Neuropsychopharmacology*. doi: 10.1016/j.euroneuro.2014.11.014.
Hindocha, C. *et al.* (2020) 'The Effectiveness of Cannabinoids in the Treatment of Posttraumatic Stress Disorder (PTSD): A Systematic Review', *Journal of Dual Diagnosis*. doi: 10.1080/15504263.2019.1652380.
Huys, D. *et al.* (2012) 'Update on the role of antipsychotics in the treatment of Tourette syndrome', *Neuropsychiatric Disease and Treatment*. doi: 10.2147/NDT.S12990.
Ilaria, R. L., Thornby, J. I. and Fann, W. E. (1981) 'Nabilone, a cannabinol derivative, in the treatment of anxiety neurosis', *Current Therapeutic Research - Clinical and Experimental*.
Jetly, R. *et al.* (2015) 'The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study', *Psychoneuroendocrinology*. doi: 10.1016/j.psyneuen.2014.11.002.
Karniol, I. G. *et al.* (1974) 'Cannabidiol interferes with the effects of Δ9-tetrahydrocannabinol in man', *European Journal of Pharmacology*. doi: 10.1016/0014-2999(74)90129-0.
Kedzior, K. K. and Laeber, L. T. (2014) 'A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies', *BMC Psychiatry*. doi: 10.1186/1471-244X-14-136.
Leweke, F. M. *et al.* (2012) 'Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia', *Translational Psychiatry*. doi: 10.1038/tp.2012.15.
Linares, I. M. *et al.* (2019) 'Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test', *Revista Brasileira de Psiquiatria*. doi: 10.1590/1516-4446-2017-0015.
Linge, R. *et al.* (2016) 'Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: Role of 5-HT1A receptors', *Neuropharmacology*. doi: 10.1016/j.neuropharm.2015.12.017.
Loflin, M. *et al.* (2014) 'Subtypes of attention deficit-hyperactivity disorder (ADHD) and cannabis use', *Substance Use and Misuse*. doi: 10.3109/10826084.2013.841251.
Lu, A. T. *et al.* (2008) 'Association of the cannabinoid receptor gene (CNR1) with ADHD and post-traumatic stress disorder', *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*. doi: 10.1002/ajmg.b.30693.
Lutz, B. *et al.* (2015) 'The endocannabinoid system in guarding against fear, anxiety and stress', *Nature Reviews Neuroscience*. doi: 10.1038/nrn4036.
Makiol, C. and Kluge, M. (2019) 'Remission of severe, treatment-resistant schizophrenia following adjunctive cannabidiol', *Australian and New Zealand Journal of Psychiatry*. doi: 10.1177/0004867418815982.
Mammen, G. *et al.* (2018) 'Association of cannabis with long-term clinical symptoms in anxiety and mood disorders: A systematic review of prospective studies', *Journal of Clinical Psychiatry*. doi: 10.4088/JCP.17r11839.
Martin, M. *et al.* (2002) 'Involvement of CB1 cannabinoid receptors in emotional behaviour', *Psychopharmacology*. doi: 10.1007/s00213-001-0946-5.
McGuire, P. *et al.* (2018) 'Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial', *American Journal of Psychiatry*. doi: 10.1176/appi.ajp.2017.17030325.
Mechoulam, R. and Parker, L. A. (2013) 'The Endocannabinoid System and the Brain', *Annual Review of Psychology*. doi: 10.1146/annurev-psych-113011-143739.
Milz, E. and Grotenhermen, F. (2015) 'Successful therapy of treatment resistant adult adhd with cannabis: Experience from a medical practice with 30 patients', *Abstract book of the Cannabinoid Conference 2015*.
Muller-Vahl, K. *et al.* (1999) 'Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol [3]', *American Journal of Psychiatry*.

Müller-Vahl, K. R. *et al.* (2002) 'Treatment of Tourette's syndrome with Δ9-tetrahydrocannabinol (THC): A randomized crossover trial', *Pharmacopsychiatry*. doi: 10.1055/s-2002-25028.
Müller-Vahl, K. R. *et al.* (2003) 'Δ9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial', *Journal of Clinical Psychiatry*. doi: 10.4088/JCP.v64n0417.
Müller-Vahl, K. R., Schneider, U. and Emrich, H. M. (2002) 'Combined treatment of Tourette syndrome with Δ9-THC and dopamine receptor antagonists', *Journal of Cannabis Therapeutics*. doi: 10.1300/J175v02n03_10.
Nutt, D. J. and Malizia, A. L. (2004) 'Structural and functional brain changes in posttraumatic stress disorder', in *Journal of Clinical Psychiatry*.
Pallanti, S. *et al.* (2002) 'Treatment non-response in OCD: Methodological issues and operational definitions', *International Journal of Neuropsychopharmacology*.
Pertwee, R. G. (2006) 'The pharmacology of cannabinoid receptors and their ligands: an overview', *International Journal of Obesity*, 30, pp. S13–S18. doi: 10.1038/sj.ijo.0803272.
Phillips, B. et al (2014) *Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009) for Evidence-based Oxford Centre Medicine – Levels of Evidence*, *Centre for Evidence Based Medicine*.
Pierre, J. M., Gandal, M. and Son, M. (2016) 'Cannabis-induced psychosis associated with high potency "wax dabs"', *Schizophrenia Research*. doi: 10.1016/j.schres.2016.01.056.
Pisanti, S. *et al.* (2017) 'Cannabidiol: State of the art and new challenges for therapeutic applications', *Pharmacology and Therapeutics*. doi: 10.1016/j.pharmthera.2017.02.041.
Pringsheim, T. *et al.* (2019) 'Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders', *Neurology*. doi: 10.1212/WNL.0000000000007466.
Roitman, P. *et al.* (2014) 'Preliminary, open-label, pilot study of add-on oral Δ9- tetrahydrocannabinol in chronic post-traumatic stress disorder', *Clinical Drug Investigation*. doi: 10.1007/s40261-014-0212-3.
Sandyk, R. and Awerbuch, G. (1988) 'Marijuana and tourette's syndrome', *Journal of Clinical Psychopharmacology*. doi: 10.1097/00004714-198812000-00021.
Sarris, J. *et al.* (2020) 'Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review', *BMC psychiatry*. doi: 10.1186/s12888-019-2409-8.
Schindler, F. *et al.* (2008) 'Improvement in refractory obsessive compulsive disorder with dronabinol', *American Journal of Psychiatry*. doi: 10.1176/appi.ajp.2007.07061016.
Schipper, R. *et al.* (2018) 'Medicinal cannabis (Bedrolite) substitution therapy in inpatients with a psychotic disorder and a comorbid cannabis use disorder: A case series', *Journal of Psychopharmacology*. doi: 10.1177/0269881117735684.
Seeman, P. (2016) 'Cannabidiol is a partial agonist at dopamine D2High receptors, predicting its antipsychotic clinical dose', *Translational psychiatry*. doi: 10.1038/tp.2016.195.
Shannon, S. and Opila-Lehman, J. (2016) 'Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report', *The Permanente journal*. doi: 10.7812/TPP/16-005.
De Souza Crippa, J. A. *et al.* (2004) 'Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow', *Neuropsychopharmacology*. doi: 10.1038/sj.npp.1300340.
Stevens, J. S. *et al.* (2017) 'Amygdala Reactivity and Anterior Cingulate Habituation Predict Posttraumatic Stress Disorder Symptom Maintenance After Acute Civilian Trauma', *Biological Psychiatry*. doi: 10.1016/j.biopsych.2016.11.015.
Strohbeck-kuehner, P., Skopp, G. and Mattern, R. (2008) 'Cannabis improves symptoms of ADHD', *Archiv*.
Szejko, N. *et al.* (2019) 'Vaporized Cannabis Is Effective and Well-Tolerated in an Adolescent with Tourette Syndrome', *Medical Cannabis and Cannabinoids*. doi: 10.1159/000496355.
Tandon, R. (2011) 'Antipsychotics in the treatment of schizophrenia: An overview', *Journal of Clinical Psychiatry*. doi: 10.4088/JCP.10075su1.01.
Thomas, A. *et al.* (2007) 'Cannabidiol displays unexpectedly high potency as an antagonist of CB 1 and CB 2 receptor agonists in vitro', *British Journal of Pharmacology*. doi: 10.1038/sj.bjp.0707133.

Thomas, H. (1996) 'A community survey of adverse effects of cannabis use', *Drug and Alcohol Dependence*. doi: 10.1016/S0376-8716(96)01277-X.
Umathe, S. N., Manna, S. S. S. and Jain, N. S. (2011) 'Involvement of endocannabinoids in antidepressant and anti-compulsive effect of fluoxetine in mice', *Behavioural Brain Research*. doi: 10.1016/j.bbr.2011.04.031.
UNODC (2016) *World drug report*, *United Nations publication*. doi: 10.1007/s13398-014-0173-7.2.
Zuardi, A. W. *et al.* (1982) 'Action of cannabidiol on the anxiety and other effects produced by δ9-THC in normal subjects', *Psychopharmacology*. doi: 10.1007/BF00432554.
Zuardi, A. W. *et al.* (1993) 'Effects of ipsapirone and cannabidiol on human experimental anxiety', *Journal of Psychopharmacology*. doi: 10.1177/026988119300700112.
Zuardi, A. W. *et al.* (1995) 'Antipsychotic effect of cannabidiol [3]', *Journal of Clinical Psychiatry*.
Zuardi, A. W. *et al.* (2006) 'Cannabidiol monotherapy for treatment-resistant schizophrenia', *Journal of Psychopharmacology*. doi: 10.1177/0269881106060967.
Zuardi, A. W. *et al.* (2009) 'Cannabidiol for the treatment of psychosis in Parkinsons disease', *Journal of Psychopharmacology*. doi: 10.1177/0269881108096519.
Zuardi, A. W. *et al.* (2017) 'Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life', *Frontiers in Pharmacology*. doi: 10.3389/fphar.2017.00259.