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A Scoping Review of the Use of Cannabidiol in Psychiatric Disorders

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Abstract

Cannabidiol (CBD) has become a fast-growing avenue for research in psychiatry, and clinicians are challenged with understanding the implications of CBD for treating mental health disorders. The goal of this review is to serve as a guide for mental health professionals by providing an overview of CBD and a synthesis the current evidence within major psychiatric disorders. PubMed and PsycINFO were searched for articles containing the terms “cannabidiol” in addition to major psychiatric disorders and symptoms, yielding 2,952 articles. Only randomized controlled trials or within-subject studies investigating CBD as a treatment option for psychiatric disorders (N=16) were included in the review. Studies were reviewed for psychotic disorders (*n* =6), anxiety disorders (*n* =3), substance use disorders (tobacco n= *3*, cannabis n= *2*, opioid n= *1*), and insomnia (n= *1*). There were no published studies that met inclusion criteria for alcohol or stimulant use disorder, PTSD, ADHD, autism spectrum disorder, or mood disorders. Synthesis of the CBD literature indicates it is generally safe and well tolerated. The most promising preliminary findings are related to the use of CBD in psychotic symptoms and anxiety. There is currently not enough high-quality evidence to suggest the clinical use of CBD for any psychiatric disorder.

Keywords

Psychiatry; Anxiety; Psychosis; Treatment; CBD; Clinicians

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1. Introduction

Cannabidiol (CBD) is a phytocannabinoid in the *Cannabis sativa* plant that has gained widespread attention for its potential use in psychiatry research due to its role as a neuromodulator in areas of the brain that control cognition, emotion regulation, behavior, and physiological responses (Bonaccorso et al., 2019; Glass et al., 1997). Conventional pharmacotherapies in psychiatry are generally effective but their use can be stigmatized, and they can confer burdensome adverse effects. Consequently, patients may seek out alternative therapies such as CBD-containing products. Mental health clinicians are now challenged to rapidly adapt to the growing body of literature regarding the use of CBD in psychiatric disorders. Accordingly, this review provides an overview of CBD, including regulatory matters and commercial use and regulatory matters; safety and tolerability; addiction potential; and its metabolism and potential drug-drug interactions. This is followed by a discussion of the current level of evidence for treating common psychiatric disorders, organized in descending order based on the quality of research available. Two tables are presented at the end of the review: one summarizes the current evidence for each condition and catalogs registered ongoing clinical trials, and the other is a guide to help answer common questions about CBD from patients and providers. This review will provide mental health clinicians with important information about CBD and an understanding of the quality of evidence for its use in common psychiatric conditions to support them in making recommendations to patients.

1.1 Overview of cannabidiol (CBD)

Cannabis sativa is a plant made up of hundreds of constituents, including more than 100 cannabinoids; the most common cannabinoids are Δ-9-tetrahydrocannabinol (THC) and CBD. THC and CBD are present in varying proportions based upon the cultivated variety of *Cannabis sativa* (ElSohly et al., 2017). Broadly, THC is the primary intoxicating constituent, whereas CBD is a non-intoxicating constituent of the plant and is generally touted for its therapeutic potential for a variety of conditions (Bhattacharyya et al., 2010; ElSohly et al., 2017; Mechoulam and Parker, 2013). CBD has many potential targets within the central nervous system. CBD has a low affinity for cannabidnoid-1 (CB1) and cannabinoid-2 (CB2) receptors, where it may act as a negative allosteric modulator of CB1 activity and a weak inverse agonist or partial agonist of CB2 receptors (Laprairie et al., 2015; Tham et al., 2019; Thomas et al., 2007). CBD also has indirect effects on endocannabinoid signaling, such as increasing levels of the endocannabinoid ligand anandamide by decreasing its cellular re-uptake by fatty acid binding proteins and decreasing endocannabinoid hydrolysis by fatty acid amide hydrolase (Elmes et al., 2015; Ligresti et al., 2016). Beyond the endocannabinoid system, CBD may modulate serotonin 5-HT_{1A} receptors, G protein-coupled receptors, and TRPV1 (transient receptor potential cation channel subfamily V member 1) receptors, as well as μ- and δ-opioid receptors (Campos et al., 2012; Pertwee, 2008). The exact mechanisms of CBD are not yet clear, and the relevance of the numerous proposed targets need to be further investigated. Nonetheless, reviews have indicated that there is a growing preclinical (Ligresti et al., 2016) and clinical (Bonaccorso et al., 2019; Khan et al., 2020) literature indicating that CBD could have antipsychotic (Batalla et al., 2019; Iseger and

Bossong, 2015; Kopelli et al., 2020), anxiolytic (Bahji et al., 2020; Skelley et al., 2020), antidepressant (Pinto et al., 2020), and anti-craving (Prud'homme et al., 2015) qualities.

1.2 Regulatory Matters and Commercial Use

The regulatory matters surrounding CBD are complex and quickly evolving. In the United States, the 2018 Farm Bill was a catalyst for the expansion of CBD products. The bill removed hemp, a cultivated variety of *Cannabis sativa* required to have less than 0.3% THC by dry weight, from the Controlled Substance Act definition of "marijuana". This made it federally legal to produce hemp-based products (Alharbi, 2020). The legality of CBD products often comes down to the variety of the *Cannabis sativa* used: cannabis (Schedule I drug; federally illegal to produce) or hemp (federally legal to produce) (Corroon and Kight, 2018); however, possessing hemp-based CBD products can still be a legal "grey area"(Alharbi, 2020; Corroon and Kight, 2018). The legal status of CBD products are further complicated by the FDA approval of Epidiolex, a purified CBD compound with no other cannabinoids or terpenoids approved as an antiepileptic treatment for two rare pediatric-onset seizure disorders, Lennox-Gastaut syndrome and Dravet syndrome (Billakota et al., 2019). See Alharbi (2020), Brunetti et al. (2020), and Vlad et al. (2020) for reviews concerning the legality of CBD in the United States and around the world.

There has been a dramatic increase in the use of commercial CBD products, with retail sales of CBD products projected to reach $16 billion by 2025 (Azer et al., 2019). CBD products can be plant- or non-plant-derived, and can be classified by their cannabinoid source profile as an isolate (pure CBD, no other cannabinoids or terpenes), full-spectrum (CBD with terpenes and other cannabinoids, including small amounts of THC), or broad-spectrum (CBD with terpenes and other cannabinoids, but not THC) (Marinotti and Sarill, 2020). CBD is manufactured as several product types that can be used in a variety of ways, including inhalation (smoking or vaping), ingestion, topical applications, sublingual, transdermal (patches), or transmucosal administration. Commercial products containing CBD are widely available, including food items, beverages, lotions, cosmetics, and oils, accessible to consumers in multiple point-of-sale locations such as online retailers, coffee shops, gas stations, health spas, and bakeries.

Commercially available CBD products are largely unregulated and are not held to the quality control as FDA-approved medications, which can result in inconsistent dosing, safety, and therapeutic response predictability (Freeman et al., 2019b). Two studies found that a majority of sampled CBD products were mislabeled regarding their CBD content, and approximately a quarter of the products contained detectable amounts of THC (Bonn-Miller et al., 2017; Lachenmeier et al., 2019).

1.3 Dosing, safety, and tolerability

Studies have indicated that CBD is generally safe and well tolerated with relatively low potential for toxicity (Organization, 2018). One study found that purified CBD (as Epidiolex) was well tolerated in healthy controls across a wide range of doses, including acute administration (up to 6000 mg) and multiple administrations daily (750 or 1500 mg, twice daily for six days) (Taylor et al., 2018). Additionally, studies in patients with epilepsy

have found CBD to be well tolerated in high doses over a longer period of time (e.g., up to 50 mg/kg/day for up to three months) (Devinsky et al., 2017; Devinsky et al., 2016; Taylor et al., 2018). Of note, these studies used purified CBD and dosing will likely differ if using whole plant, full-spectrum, or even broad-spectrum CBD products.

The overall safety profile of CBD appears to compare favorably with many psychiatric medications (Boggs et al., 2018; Iffland and Grotenhermen, 2017; Leweke et al., 2012; Machado Bergamaschi et al., 2011; McGuire et al., 2018). In clinical trials for Epidiolex in epilepsy (10 mg/kg/day vs. 20 mg/kg/day), adverse events included transaminase elevations (8%, 16%), sedation (41%, 51%), decreased appetite (16%, 22%), diarrhea (9%, 20%), sleep disturbance (5%, 11%), infections (41%, 40%), pneumonia (8%, 5%), viral infections (7%, 11%), and weight loss (3%, 5%) (Brown and Winterstein, 2019). It is important to note that the elevated transaminase levels were most likely due to a drug-drug interaction with valproic acid (Chesney et al., 2020; Devinsky et al., 2016). Another review and meta-analysis (n=13) of clinical trials across multiple clinical populations (epilepsy n=5, schizophrenia n=2, cannabis use n=1, Huntington's disease n=1, type II diabetes n=1, non-alcoholic fatty liver disease n=1, Crohn's disease n=1) or healthy controls (n=1) found that only diarrhea remained as an adverse event when excluding studies in childhood epilepsy (Chesney et al., 2020). Gastrointestinal adverse events are the most likely side effect of CBD use in patients without epilepsy. Animal studies have indicated that CBD may have negative effects on fertility, particularly in males, although additional research is needed to make any definitive claims about this effect in humans (Carvalho et al., 2020; O'Llenecia et al., 2019). Animal studies in mice and zebrafish have also indicated that CBD may have teratogenic effects (e.g., physical deformities, decreased weight and length, behavioral abnormalities, and change in developmental biomarkers) (Achenbach et al., 2018; Ahmed et al., 2018; Carty et al., 2019; Carty et al., 2018; Fish et al., 2019); however, one study did not find any teratogenic effects of CBD (Brigante et al., 2018) and no studies have examined whether these effects occur in humans. More research on the effects of CBD prenatally, perinatally, and postnatally is critical before clinicians can recommend CBD during pregnancy.

1.4 Abuse liability

The World Health Organization has reported that pure CBD is not related to effects that indicate misuse, abuse, or dependence potential (Organization, 2018). One randomized double-blind, placebo-controlled eight-week study of 31 frequent cannabis smokers examined weekly use of differing doses (200, 400, 600, and 800 mg) of oral, non-plant derived CBD and inhaled cannabis (THC 5.3–5.8%) and found that CBD had no greater abuse-related liability than placebo when comparing participant ratings of "feeling high", "feeling good", and suggested street value (Babalonis et al., 2017). Another randomized, double-blind, placebo-controlled study of 43 polydrug users found that a therapeutic dose (750 mg) of highly purified CBD (Epidiolex) did not confer a significant abuse liability in this highly sensitive population. However, supratherapeutic doses (1500 and 4500 mg) demonstrated detectable subjective effects compared to placebo, but this was significantly less than 10 mg and 30 mg of dronabinol (synthetic THC), as well as 2 mg of alprazolam (Schoedel et al., 2018). Abrupt withdrawal of CBD after 4-weeks of use (750 mg twice daily taken orally) did not result in any symptoms of physical withdrawal (Taylor et al., 2020).

Route of administration may also be important. One study found that vaporized CBD (100 mg) had significantly higher subjective rating for “drug effect”, “pleasant”, and “like drug” as compared to oral CBD (100 mg) (Spindle et al., 2020). Another study found that vaporized CBD (400 mg) had some subjective intoxicating properties (e.g., “feeling stoned”, dissociated state) as compared to placebo (Solowij et al., 2019). However, an earlier study reported that 16 mg of vaporized pure CBD did not impact subjective effects (Hindocha et al., 2015). Given the clinical findings, CBD does not seem to present with a pharmacological profile of a drug of abuse, but more research is needed to better understand how routes of administration and dose may confer abuse liability (i.e., vaporized CBD).

1.5 Metabolism and drug-drug interactions

CBD is metabolized in the liver by the cytochrome P450 pathway and uridine 5’-diphosoglucuronosyltransferase (UGT), where it is metabolized to the active metabolite 7-OH-CBD by CYP2C19 and then to inactive metabolites by CYP3A4 and UGT (Harvey and Mechoulam, 1990; Huestis, 2005; Ujváry and Hanuš, 2015). This first pass metabolism results in variable bioavailability (Landmark and Brandl, 2020; White, 2019), which is directly impacted by the pharmacokinetics and absorption profiles of the route of administration. Bioavailability can also be strongly influenced by factors such as co-ingested food (e.g., high fat meals increase bioavailability) or variations in vaping habits when using vaporized CBD (Landmark and Brandl, 2020; Vandrey et al., 2017). Epidiolex (purified CBD) reaches maximal concentration 2.5 to 5 hours after oral administration, and has an elimination half-life of 56 to 61 hours (White, 2019). A systematic review of the pharmacokinetics of commercial CBD products in humans found the half-life of CBD was 1.4 to 10.9 hours after oromucosal spray, 2 to 5 days after oral administration, 24 hours after intravenous administration, and 31 hours after smoking (Millar et al., 2018).

There is limited research concerning drug-drug interactions between CBD and other medications. CBD may have many theoretical drug-drug interactions since the CYP3A and CYP2C enzymatic families are implicated in metabolizing various medications and other substances. A comprehensive review was recently published detailing such potential interactions (Balachandran et al., 2021). Case studies have indicated that psychiatric medications (lithium) and other medications (tacrolimus and methadone) may have drug-drug interactions with CBD (Leino et al., 2019; Madden et al., 2020; Singh et al., 2020); however, clinical studies investigating these specific effects are lacking. Of note, while lithium is not metabolized by the liver, some evidence has indicated that CBD can increase creatinine levels and cause renal dysfunction which negatively affects lithium metabolism, potentially leading to toxicity (Singh et al., 2020).

Patients with underlying liver disease or who are concurrently taking other medications that adversely affect the liver should be aware of potential elevations in transaminases. A recent phase 1, open-label study in 16 healthy adults found that a therapeutic dose of CBD (1500 mg/day) over almost four weeks resulted in increased serum alanine aminotransferase in seven participants (44%), and reached the level for drug-induced liver injury for five participants (31%) (Watkins et al., 2020). A dose-dependent increase in serum aminotransferases was found in childhood epilepsy clinical trials where a majority or all the

patients affected were concurrently taking valproic acid (Devinsky et al., 2017; Devinsky et al., 2018; Thiele et al., 2018). CBD has been shown to increase concentration levels of antiepileptic drugs, such as clobazam, topiramate, and zonisamide (Landmark and Brandl, 2020); however, other studies have reported no evidence of CBD interaction with clobazam (VanLandingham et al., 2020). Prescribers of psychiatric medications should discuss with patients that CBD has the potential for drug interactions, particularly since CBD is typically used as an adjunct to other psychiatric medications (Corroon and Phillips, 2018).

2. Methods: evidence for CBD use in major psychiatric disorders

To review the use of CBD for major psychiatric disorders, PubMed and PsychINFO searched for articles published up to April 2021 with abstracts and titles containing the terms “cannabidiol” or “CBD,” in addition to: “psychiatry,” “psychiatric,” “anxiety,” “post-traumatic stress disorder,” “sleep,” “insomnia,” “bipolar disorder,” “mania,” “mood disorder,” “depression,” “major depressive disorder,” “obsessive-compulsive disorder,” “psychosis,” “schizophrenia,” “autism,” “substance use,” “alcohol,” “alcohol use disorder,” “cannabis use disorder,” “nicotine,” “nicotine use disorder,” “tobacco,” “opioid,” “amphetamine,” “stimulant,” “benzodiazepine,” and “attention-deficit hyperactivity disorder.” This search strategy yielded 2,952 articles, which were then limited to clinical trials and randomized controlled trials (PubMed n=139, PsycINFO n=41) in English to be reviewed for inclusion. After eliminating duplicates, only double-blind randomized controlled trials or within-subjects trials using CBD as a monotherapy or adjunct treatment for a diagnosed psychiatric disorder were included (N=16, see Table 1 for details). Studies investigating any combination of CBD and THC were excluded. Systematic reviews (with or without meta-analysis) were used for systematic snowballing. There were no limitations set for year of publication or age of the patient populations.

The clinical trials registered on Clinicaltrials.gov (as of April 20, 2021) are described at the end of each psychiatric disorder section and listed in Table 1. These are subject to change.

3. Results

3.1 Psychotic Disorders

There is a growing body of evidence that the endocannabinoid system is implicated in the pathophysiology of psychosis (Bossong et al., 2014; Zamberletti et al., 2012), thus CBD has been proposed as a candidate pharmacotherapy (Davies and Bhattacharyya, 2019). Preclinical work indicates that CBD inhibits the degradation of anandamide (Bisogno et al., 2001), an endocannabinoid which plays a major role in mood regulation, cognition, and behavior (Di Marzo and Petrosino, 2007). Indeed, increased levels of anandamide has been associated with reduced psychotic symptoms in humans after CBD administration (more details on this study below) (Leweke et al., 2012), which provides clinical support for this mechanisms of action. Modulation of glutamate, which has been noted in preclinical work (Linge et al., 2016), may also be a potential mechanism for the antipsychotic effects of CBD. A recent study in humans found that a single dose of CBD (600 mg) increased glutamate within the hippocampus of individuals with early psychosis (n=13) as compared to placebo. There was a negative association between hippocampal glutamate level and the

severity of psychosis symptoms, but this was not dependent on treatment (CBD v. placebo) (O'Neill et al., 2021).

The use of whole plant cannabis products with considerable THC content is likely a risk factor for the development of psychosis in vulnerable individuals (Marconi et al., 2016; Schoeler et al., 2016). There is some evidence suggesting that CBD may mitigate the psychotomimetic effects of THC (Englund et al., 2013; Morgan and Curran, 2008; Schubart et al., 2011); however, no randomized clinical trials have been conducted on the utility of CBD as a treatment for THC-induced psychosis. The acute effects of CBD on THC have been reviewed elsewhere (Freeman et al., 2019a).

Currently, there are six published studies examining the effects of CBD within psychotic disorders as a monotherapy (n=1) or an adjunct therapy (n=5). The monotherapy study was a four-week randomized, double-blind, parallel group trial which investigated a maximum of 800 mg daily of purified CBD as compared to a maximum of 800 mg of amisulpride (second generation antipsychotic) daily for patients with schizophrenia (n=42). Both treatment arms had a comparable improvement in Positive and Negative Syndrome Scale (PANSS) scores, but patients randomized to the CBD arm reported a much more favorable side effect profile, lacking adverse reactions such as extrapyramidal symptoms, weight gain, and hyperprolactinemia. Clinical improvement was accompanied by a significant increase in levels of serum anandamide, as noted above (Leweke et al., 2012). Notably, the patients in this study were included only if they had an acute exacerbation of symptoms, resulting in higher baseline PANSS scores compared to the adjunct CBD studies below.

Other studies have examined purified CBD as an adjunct treatment for psychosis. A randomized, double-blind, placebo-controlled study examined the use of 1000 mg CBD adjunct therapy in 43 outpatients with schizophrenia, as compared to 45 patients without adjunct CBD, over the course of six weeks. Adjunct CBD led to a significant improvement in psychotic symptoms and clinical impression as measured by the PANSS and Clinical Global Impression Scale, in addition to approaching significance in overall functioning (McGuire et al., 2018). However, a similar six-week double blind, placebo-controlled randomized trial examined the use of 600 mg CBD daily as adjunct treatment for 36 patients with schizophrenia (CBD n=18) and found that CBD was no more effective than placebo (n=18) in treating psychotic symptoms (Boggs et al., 2018). Between these two adjunct studies, both sets of participants had similar baseline PANSS scores and mean age (40s); however, the null study used a lower dose of CBD (300–600 mg) and participants had a more chronic course of illness. Lastly, two recent double-blind, placebo-controlled crossover studies of the same 15 patients with early psychosis reported a reduction in the average total PANSS score (O'Neill et al., 2021) during an acute dose of adjunct CBD (600 mg), as compared to placebo, but this result was only trending when comparing the change in median total PANSS score (O'Neill et al., 2020). There were no differences between CBD and placebo for change in average positive symptoms, negative symptoms, or the State Trait Anxiety Inventory state subscale (O'Neill et al., 2020; O'Neill et al., 2021).

Cognition is also adversely affected in psychosis (Osborne et al., 2017); however, evidence has not supported CBD as a pro-cognitive treatment. A double-blind, placebo-controlled

study found that among 28 patients with schizophrenia (n=13 taking antipsychotic medication), an acute dose of 300 mg or 600 mg CBD had no effect on selective attention when performing the Stroop Color Word Test, a neuropsychological test of inhibitory control. Each group showed a reduction in errors after contingency administration as compared to baseline testing, indicating a learning effect (Hallak et al., 2010). Mirroring the PANSS results detailed above, one study found no cognitive benefits of CBD (600 mg; six weeks and acute dosing, respectively) (Boggs et al., 2018; O'Neill et al., 2020), while another identified trends towards improved overall cognition (1000 mg; six weeks) (McGuire et al., 2018).

Overall, there is mixed evidence for the use of CBD for treatment of psychotic symptoms (based on PANSS), with three positive (Leweke et al., 2012; McGuire et al., 2018; O'Neill et al., 2021) and two null findings published (Boggs et al., 2018; O'Neill et al., 2020), and no evidence for CBD improving cognitive symptoms in patients with psychotic disorders (Boggs et al., 2018; Hallak et al., 2010; McGuire et al., 2018; O'Neill et al., 2020). Well-designed randomized controlled clinical trials are needed to better understand the potential role for CBD as an antipsychotic therapy. There are currently 13 clinical trials registered on Clinicaltrials.gov investigating CBD as a treatment for psychotic disorders.

3.2 Anxiety Disorders

Preclinical and clinical studies have indicated that THC and CBD may have various effects on anxiety, with THC being bi-modal (anxiolytic or anxiogenic) and CBD being considered an anxiolytic (Degroot, 2008). Based on preclinical studies, CBD may impart its anxiolytic properties through indirect modulation of the CB1 receptor (Pertwee, 2008) and enhanced anandamide levels (Bisogno et al., 2001), 5-HT_{1A} agonism (Zanelati et al., 2010), or through effects on GABA (Bakas et al., 2017; Jones et al., 2012). For a detailed review of possible anxiogenic mechanisms from preclinical and clinical work, see review by Blessing et al. (Blessing et al., 2015). CBD has also been found to follow a bell-shaped response curve for anxiety, where relatively lower and higher doses do not significantly impact anxiety while mid-range doses do (Campos and Guimarães, 2008).

Thus far, no large-scale randomized clinical trials assessing CBD as a treatment for anxiety disorders have been published; however, there have been three small-scale studies (acute dosing n=2, four-week dosing n=1) indicating its potential utility in social anxiety disorder. One double-blind, randomized controlled trial of participants with social anxiety disorder investigated the effects of encapsulated pure CBD powder (600 mg; n=12) or placebo (n=12) on subjective anxiety, self-evaluation, and physiological measures of stress while performing a simulated public-speaking task as compared to 12 healthy controls without social anxiety who did not take either CBD or placebo. Among those with social anxiety, CBD was related to significantly reduced anxiety and discomfort in speech performance and less negative self-evaluations of performance compared to those who took placebo. Additionally, the use of CBD in this group did not result in any adverse cognitive effects. Furthermore, there were no significant differences in anxiety or discomfort between the socially anxious group who took CBD and control group without a diagnosis of social anxiety during speech anticipation or after the speech was completed, indicating a therapeutic effect on anxiety-

levels for those with social anxiety. The CBD group showed increased anxiety during the speech as compared to healthy controls, but it was significantly lower than the socially anxious group who received placebo (Bergamaschi et al., 2011). Another double-blind, placebo-controlled crossover neuroimaging study found that an acute dose of CBD (400 mg) reduced subjective anxiety ratings (60, 75, and 140 minutes after administration) in a small sample of individuals with social anxiety disorder (n=10), which corresponded with reduced cerebral blood flow in fear and anxiety related brain regions (e.g., amygdala, hippocampus, hypothalamus, and cingulate cortex) (Crippa et al., 2011).

The effects of CBD on anxiety have also been tested beyond acute dosing. In a double-blind, placebo-controlled study of 37 adolescents (ages 18–19) with social anxiety disorder, participants were given 300 mg daily of CBD oil or placebo for four weeks (Masataka, 2019). CBD significantly decreased anxiety symptoms compared to placebo, and the magnitude of anxiety reduction was equivalent to a separate 26-week trial of paroxetine (the most effective medication for social anxiety disorder) using the same rating scales (Nordahl et al., 2016).

There is preliminary evidence that CBD may be helpful as an anxiolytic for social anxiety disorder; however, only three studies have examined these effects with randomized controlled trials and the sample sizes were small (Ns= 10, 36, 37) (Bergamaschi et al., 2011; Crippa et al., 2011; Masataka, 2019). There are currently nine clinical trials registered that are investigating CBD as a treatment option for anxiety, including social anxiety disorder, generalized anxiety disorder, panic disorder, and state-based anxiety (e.g., medical and testing anxiety).

3.3 Substance Use Disorders

Cannabinoid receptors are densely located in areas of the brain related to reward function and the development and maintenance of addictive behaviors (Glass et al., 1997). The endocannabinoid system has been implicated in the pathophysiology of addiction by modulating pathways that affect drug-seeking behaviors, cravings, withdrawal, and memory and emotional processes (Parsons and Hurd, 2015; Stern et al., 2018).

3.3.1 Tobacco Use Disorder—There have been three studies assessing the impact of CBD in tobacco use disorder. One randomized, double-blind, placebo-controlled study of 24 smokers with express intention to reduce smoking found that ad hoc inhalation of 400 mg of CBD reduced cigarette smoking by almost 40% over one week but did not have any effect on cravings (Morgan et al., 2013). Another randomized, double-blind, crossover study of 30 non-treatment-seeking cigarette smokers found that after an evening of abstinence from cigarette smoking, 800 mg of pure non-plant derived CBD reduced the salience and pleasantness of cigarette cues but did not have any effects on craving or withdrawal (Hindocha et al., 2018b), nor did it improve impulsivity (Hindocha et al., 2018a). There are currently no clinical trials registered examining the effects of CBD on tobacco use.

3.3.2 Cannabis Use Disorder—There have been several studies which have investigated the use of cannabinoids for treating the symptoms of cannabis use disorder (CUD); however, most of these studies used combinations of THC and CBD and will not

be reviewed here (Allsop et al., 2014; Morgan et al., 2010a; Morgan et al., 2010b; Trigo et al., 2018; Trigo et al., 2016). There are currently two published studies investigating CBD to reduce cannabis use. The first was a double-blind, placebo-controlled randomized within-subjects study of non-treatment-seeking cannabis smokers (n=31) which found that pretreatment with CBD (200, 400, or 800 mg) did not have any effects on the reinforcing or positive subjective effects of subsequently smoked cannabis (Haney et al., 2016). A recent phase 2a double-blind, placebo-controlled randomized adaptive Bayesian trial had more promising results within individuals with CUD who wanted to stop cannabis use (n=84). Phase 1 found that 400 mg (n=12) and 800 mg (n=12) of CBD in gelatin capsules was more efficacious (end points: reduced urinary THC-COOH:creatine ratio, increased days per week abstinent) than 200 mg of CBD (n=12) or placebo (n=12) after four weeks. Phase 2 found that both 400 mg (n=24) and 800 mg (n=23) of CBD exceeded primary endpoint criteria for both reduced THC-COOH:creatine ratio and days per week abstinent as compared to placebo (n=23). Even though both doses were significantly different from placebo for the primary endpoints, there was only an increase of 0.48 and 0.27 days per week abstinent for each dose, which may not be clinically relevant (Freeman et al., 2020). There are currently seven registered clinical trials that are investigating CBD in relation to cannabis use.

3.3.3 Opioid Use Disorder—In humans, one double-blind, placebo-controlled crossover study in healthy subjects found that 400 mg and 800 mg of 99% pure CBD could be safely co-administered with intravenous fentanyl (Manini et al., 2015). An exploratory double-blind, placebo-controlled study in drug-abstinent participants with heroin use disorder assessed the effects of CBD (400 or 800 mg Epidiolex) administered daily for three days on acute (one, two, and 24 hours after first dose) and protracted (one week after daily administration was completed) drug-cue induced cravings. Both doses of CBD attenuated cue-induced anxiety and cravings acutely and during the protracted testing session; however, there was no effect on general craving outside of the cue-induced task (Hurd et al., 2019). There are currently seven clinical trials registered to assess the effects of CBD in opioid use.

3.3.4 Alcohol Use Disorder—There have been no clinical trials examining the use of CBD alone in humans for alcohol use disorder. A review of CBD as a novel candidate pharmacotherapy for alcohol use disorder has been recently published (Turna et al., 2019). There are currently five clinical trials registered for the effects of CBD in alcohol use disorder, including the effects on withdrawal symptoms and comorbidity with PTSD.

3.3.5 Stimulant Use Disorder—Preclinical evidence has shown that CBD may modify stimulant use by reducing self-administration motivation and impair reconsolidation of drug-related memories (Calpe-López et al., 2019). However, there is currently no published evidence supporting the use of CBD in treating stimulant use disorders in humans, and currently there are no registered clinical trials.

Overall, clinical work has resulted in limited and mixed findings for the use of CBD in substance use disorders. Currently registered clinical trials will help clarify any treatment potential of CBD in cannabis, opioid, and alcohol use disorders.

3.4 Insomnia

The sedative effects of CBD are dose-dependent, where low doses appear to promote wakefulness and higher doses have sedating effects (Babson et al., 2017). Even though sedation is a commonly reported adverse event from CBD administration, there is only one published study examining CBD in insomnia. The double-blind, placebo-controlled study of 15 participants with insomnia found that 160 mg of CBD significantly increased subjective reporting of sleep duration (>7 hours) compared to placebo, while doses of 40 mg and 80 mg did not incur the same sleep benefits. There were no significant differences in sleep latency, sleep interruptions, or subjective quality of sleep and dream recall was reduced (Carlini and Cunha, 1981). The preliminary evidence of the sedative effects of CBD is weak and under-powered. There is currently one clinical trial registered to further this line of research.

3.6 Post-Traumatic Stress Disorder

Preclinical studies have shown that the endogenous cannabinoid system can attenuate fear responses by disrupting traumatic memory acquisition and consolidation, as well as enhancing traumatic memory extinction (Bitencourt and Takahashi, 2018). Although human studies suggest CBD has the ability to modulate neurobiological processes involved in fear conditioning and fear memory processes (Das et al., 2013), there have been no data published from randomized, placebo-controlled trials to date. Other evidence for treating PTSD with cannabinoids (CBD, THC, synthetic THC analogues) is reviewed elsewhere (Hindocha et al., 2020). There are currently four clinical trials registered examining the utility of CBD in treating PTSD.

3.7 Autism Spectrum Disorder

In humans, there have been two studies which suggest a role for CBD in treating symptoms of autism such as self-injury, insomnia, social deficits, and anxiety (Barchel et al., 2019; Fleury-Teixeira et al., 2019); however, both studies used CBD preparations that contained THC. One study in adults with and without autism spectrum disorder examined the effects of an acute dose of CBD (600 mg) on functional connectivity in the brain, but clinically relevant items (e.g., symptom response) were not reported (Pretzsch et al., 2019). There are currently no published randomized controlled trials for the use of CBD alone in treating autism spectrum disorder, but there are five registered ongoing clinical trials.

3.8 Attention-Deficit/Hyperactivity Disorder

The endocannabinoid system has been implicated in executive functioning, which may make CBD a theoretical treatment option for ADHD (Bossong et al., 2013). Presently, there are no randomized controlled studies examining the effects of CBD alone in ADHD, and no clinical trials have been registered.

3.9 Mood Disorders

There have been no human studies that have assessed the effectiveness of CBD where the primary outcome is treating a mood disorder, but there are three clinical trials currently registered to investigate CBD as a treatment for mood disorders (bipolar disorder and treatment resistant depression).

4. Discussion

Overall, CBD presents as a generally safe and well-tolerated pharmacotherapy with limited abuse liability making it a popular candidate treatment for psychiatric conditions. Psychiatric symptoms are among the most commonly reported reasons for commercial CBD use (Corroon and Phillips, 2018), despite a lack of randomized controlled trials to support their use (see Table 1 for overview). Even the psychiatric disorders with the most promising findings and the largest number of published studies, such as psychotic and anxiety disorders, currently have inadequate data to make a decision on the efficacy of CBD as a treatment option, while other disorders are wholly lacking high-quality research (e.g., PTSD, ADHD, and mood disorders). The heterogeneous studies described in this clinical guide had several limitations such as small sample sizes, brief treatment periods, variable dose ranges (40 mg – 1000 mg), inconsistent product types, concurrent or inconsistent use of other psychiatric medications, and/or lack of comparable control groups.

Furthermore, many clinically relevant questions need to be properly addressed. The dose-response of CBD must be elucidated, as evidenced in the differing effects in doses treating anxiety (i.e., bell-shaped response) and psychosis (i.e., discrepant findings between McGuire and Boggs). More research is also needed to understand variations in dosing and clinical outcomes between purified (e.g., Epidiolex) and full-spectrum CBD products. A meta-analysis of observational studies in treatment refractory epilepsy found that patients taking CBD-rich extract had better results, even at lower doses, than those taking purified CBD (Pamplona et al., 2018). Single extracted plant-derived or purified compounds, like Epidiolex, are used most often in clinical research, while full-spectrum CBD products derived from hemp are more commonly used outside of research (Pamplona et al., 2018), which may result in varying or dose-dependent effects on psychiatric symptoms. Mental health clinicians must exercise caution when recommending CBD given its potential for many medication interactions (Balachandran et al., 2021; Brown and Winterstein, 2019), as well as transient elevations in liver enzymes identified in healthy controls (Watkins et al., 2020). Mental health professionals and patients must also be particularly aware of the lack of regulation of CBD products, as many products are mislabeled and may also contain THC (Bonn-Miller et al., 2017). Another important clinical question revolves around the use of CBD in the pediatric population. Although Epidiolex has been FDA-approved for children, at this time, the use of commercial CBD products is not recommended for children given the lack of longitudinal data in this population and limited evidence regarding the potential consequences of non-intoxicating cannabinoids on the developing human brain. Additionally, there is limited emerging evidence from preclinical studies that CBD may be teratogenic; however, evidence of this from human studies is lacking.

In conclusion, there is currently not enough quality evidence to make a recommendation for the use of CBD in any psychiatric disorder. Well-designed, properly powered, and longitudinal preclinical and clinical studies are needed (many of which are underway) and may reveal a role for CBD in the treatment of certain psychiatric disorders where there is currently a signal for efficacy, such as psychosis or anxiety. There are currently 54 ongoing registered clinical trials examining the effect of CBD across most psychiatric conditions reviewed (see Table 1). A summary table of frequently asked questions is included as

a helpful guide for clinicians when addressing CBD-related questions with patients and families (see Table 2).

Declaration of interests:

Dr. Wilens has been or is a consultant for Arbor Pharmaceuticals, Otsuka, Ironshore, KemPharm, Vallon, Gavin Foundation, Bay Cove Human Services, US National Football League (ERM Associates), and US Minor/Major League Baseball. Dr. Wilens has published books: Straight Talk About Psychiatric Medications for Kids (Guilford Press); and co/edited books ADHD in Adults and Children (Cambridge University Press), Massachusetts General Hospital Comprehensive Clinical Psychiatry (Elsevier) and Massachusetts General Hospital Psychopharmacology and Neurotherapeutics (Elsevier). Dr. Wilens is co/owner of a copyrighted diagnostic questionnaire (Before School Functioning Questionnaire). Dr. Gruber has pending and ongoing studies sponsored by Foria/Praxis Ventures and Charlottes Web; has consulted for Greenwich Biosciences; has received honorarium from National Academy of Neuropsychology; and has edited for the Harvard community. Dr. Gray, Dr. Squeglia, Dr. Kirkland, and Dr. Fadus report no potential conflicts or competing financial interests.

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Highlights:

- Cannabidiol (CBD) is a phytocannabinoid in the *Cannabis sativa* plant that has gained widespread attention for its potential role in psychiatry research
- Mental health clinicians are now challenged to rapidly adapt to the growing body of literature regarding the use of CBD in psychiatric disorders
- Upon review for the literature, the most promising preliminary findings are related to the use of CBD in psychotic symptoms and anxiety
- There is currently not enough high-quality evidence to suggest the clinical use of CBD for any psychiatric disorder
- Summary tables of the current clinical evidence and frequently asked questions are included as a guide for mental health practitioners

Table 1.

Overview of Published and Pending Clinical Trials for Psychiatric Disorders

Psychiatric Disorder	Studies & Participants	Dose Range (mg)	Route	Treatment time	Adverse Events	Overall Effects	Registered on Clinicaltrials.gov**
Psychotic Disorders	6 (N=190) *	300–1000	Oral	Acute – 6 wks	Sedation (n=1); Mild GI discomfort, dyslipidemia, nausea (n=1); Not Reported (n=3)	Mixed (3 positive, 3 null ***)	13
Anxiety Disorders	3 (N=83)	300–600	Oral	Acute – 4 wks	None (n=2), Not Reported (n=1)	Positive	9
Tobacco Use Disorder	3 (N=54) *	400 800	Inhaled Oral	7 days Acute	None (n=1); Not Reported (n=2)	Mixed (2 positive, 1 null)	0
Cannabis Use Disorder	2 (N=115)	200, 400, 800	Oral	Acute – 4 weeks	GI, headache, anxiety, fatigue, cold symptoms, pain, increased heart rate	Mixed	7
Opioid Use Disorder	1 (N=42)	400, 800	Oral	3 days	None	Positive	7
Alcohol Use Disorder	0	N/A	N/A	N/A	N/A	N/A	5
Stimulant Use Disorder	0	N/A	N/A	N/A	N/A	N/A	0
Insomnia	1 (N=15)	40, 80, 160	Oral	Acute	Not Reported	Mixed	1
PTSD	0	N/A	N/A	N/A	N/A	N/A	4
ASD	0	N/A	N/A	N/A	N/A	N/A	5
ADHD	0	N/A	N/A	N/A	N/A	N/A	0
Mood Disorders	0	N/A	N/A	N/A	N/A	N/A	3
Total	16 trials (N=499)	40–1000 mg	Oral (n=15) Inhaled (n=1)	Acute-6 weeks	Minimal side effects	9 positive, 4 null, 3 mixed	54 registered trials

* Two publications from the same clinical trial. Subjects included once in total N for psychosis (n = 15; Refs. O'Neill et al., 2020 and O'Neill et al., 2021) and tobacco use disorder (n = 20, Refs. Hindocha et al., 2018a and Hindocha et al., 2018b).

** As of April 20, 2021. Subject to change.

*** Results from O'Neill et al. (2020) were trending towards positive for change in median total PANSS.

Table 2.

Commonly Asked Questions from Clinicians and Patients

What is the difference between CBD, medical marijuana/cannabis, and hemp?	CBD is a cannabinoid found in cannabis and hemp plants in varying amounts. CBD is considered a primary, non-intoxicating constituent. The terms “medical cannabis” or “medical marijuana” generally refer to use of the cannabis plant or cannabinoids to treat medical conditions or alleviate symptoms. It is a broad term and does not refer to a specific dose or cultivar of cannabis, and it does not specifically refer to a cannabis-based product that is FDA-approved. Medical cannabis/marijuana has varying amounts of cannabinoids, including CBD. Hemp is a species of *Cannabis Sativa L.* plant that was originally cultivated for industrial use. By definition, hemp contains <0.3% THC by dry weight in the United States. Hemp often contains larger amounts of CBD than other cannabis plants. For this reason, hemp has more recently been cultivated specifically to make CBD products. CBD is extracted from hemp using several different processes to be used in a variety of product types (e.g., CBD oils, edibles, topicals). CBD can also be extracted from other varieties of the cannabis plant (those containing >0.3% THC). The total amount of CBD or THC in a product is also related to the extraction and manufacturing process.
Where are most CBD and hemp products obtained?	CBD products made from cannabis must be sold at a dispensary, while hemp-based products are sold in stores or online but may also be sold in dispensaries. Although it is possible to manufacture synthetic or non-plant derived versions of CBD, these products are generally not currently available to medical cannabis patients/consumers.
Is CBD approved by the FDA?	Currently, the only CBD-containing product approved by the FDA is Epidiolex; a plant-derived, highly purified form of CBD. Epidiolex is an unscheduled substance that has been approved for the treatment of two rare, intractable pediatric onset seizure disorders, Lennox Gastaut syndrome and Dravet Syndrome (Billakota et al., 2019).
Do you need a prescription for CBD products? What about medical cannabis?	Prescriptions are required for FDA-approved medications, and therefore are required for Epidiolex. Prescriptions cannot be written for commercial CBD products. Cannabis or any products derived from cannabis require a certification or recommendation (not a prescription) for use from a physician to access products from medical dispensaries. However, a certification or recommendation from a physician is not required to purchase CBD products that are derived from hemp (less than 0.3% THC by weight).
What conditions are people using commercially available CBD products to treat?	The most commonly reported conditions are chronic pain, arthritis/joint pain, anxiety, depression, insomnia/sleep disorders, headache, PTSD, ADHD, nausea, and skin care, among many others (Corroon and Phillips, 2018; Poll, 2020).
What are the most common ways that people use CBD?	The most common ways to use CBD include sublingual, vaping, capsule/pill, smoking, edibles, infused beverages, as well as topical lotions and ointments (Corroon and Phillips, 2018).
How did CBD become so popular?	There has been an evolving acceptance of cannabis and cannabis-related products. The last decade has seen an increase in interest in CBD particularly. The 2018 Farm Bill separated hemp from the definition of “marijuana”, which permitted the sale of hemp products and created an expansion of commercially available CBD products. The FDA approval of Epidiolex, a specific formulation of highly purified CBD for pediatric epilepsy, also sparked interest and underscored the possibility of treating other medical conditions.
Is CBD addictive?	CBD at moderate doses (200–800 mg) has not been shown to have significant addiction liability (Babalonis et al., 2017). One study showed that at very high doses (1500 mg and 4500 mg), CBD may have some subjective effects compared to placebo. This finding was much less than dronabinol (synthetic THC) and alprazolam (Schoedel et al., 2018), but more research is needed. Route of administration may also change the addiction potential of CBD, as vaporized CBD has been reported to confer subjective effects of “feeling stoned” (Solowij et al., 2019), pleasantness, or drug-liking (Spindle et al., 2020).
If a CBD product also contains THC, will the THC show up on a drug test?	This depends greatly on how much THC is in a CBD product, which is often unknown/not indicated or incorrectly indicated on a label (Bonn-Miller et al., 2017). Consistent, continued use of high-CBD, with even *very* low THC content, may lead to a positive drug test for THC. In a recent study, 50% of participants tested positive for THC on a drug test after four weeks of using a full-spectrum, high CBD product (1.04% CBD, 0.02% THC) (Dahlgren et al., 2021). This effect can depend on many variables such as patterns of use and individual pharmacokinetics. There is no way to be certain that the use of commercial CBD products will not affect a drug test.
Where are people getting information about CBD?	Many people are not accessing information that is evidence-driven and peer-reviewed, and most consumers (76%) of CBD report that they learned about it from their own internet research, family members, or friends (Corroon and Phillips, 2018).
Are there any adverse side effects associated with using CBD?	There are potential adverse side effects when using high doses of CBD, but broadly, CBD has a favorable side effect profile (Iffland and Grotenhermen, 2017), particularly when compared to many psychiatric medications. In clinical trials, which have primarily used single, extracted CBD study products (thus requiring higher doses relative to commercially available CBD products), nearly half of all study subjects reported an adverse event associated with use, including transaminase elevations, sedation and fatigue, diarrhea, sleep disturbances, and weight loss (Brown and Winterstein, 2019). However, when pediatric epilepsy was removed from the reviewed studies, only diarrhea remained as an adverse event (Chesney et al., 2020). There is also the chance of drug-drug, herb, or other dietary supplement interactions. Importantly, some CBD products may contain THC which can lead to psychoactive effects.

How regulated are commercially available CBD products? Are they safe?	Commercially available CBD products are not regulated or overseen by the FDA and are not held to the same standards as Epidiolex. They lack the consistent dosing, safety, and therapeutic response studies required for FDA-approved treatments (Freeman et al., 2019b). Many products are mislabeled with regard to CBD content and may contain higher than expected amounts of THC (Bonn-Miller et al., 2017). Studies have indicated that purified CBD as Epidiolex is generally safe and well tolerated (Organization, 2018); however, there is less known about the safety of commercially available products due to the aforementioned reasons.
Should I recommend a patient to use whole plant cannabis products with a higher CBD: THC content?	Given the lack of randomized controlled clinical trials, clinicians treating patients with psychiatric disorders should recommend that patients abstain from cannabis use (particularly cannabis with significant THC content). For patients who plan to continue their use, the most important recommendation is that they use products with the lowest possible THC content as a harm reduction strategy to mitigate some of the psychomimetic effects of THC.
Is CBD safe with other psychiatric medications?	There are potential drug-drug interactions that can occur when using CBD with psychiatric medications due to the metabolism of CBD (and other cannabinoids) in the liver (Brown and Winterstein, 2019; Rong et al., 2018; Stout and Cimino, 2014). However, the extent of these interactions in humans remains unclear. Patients with underlying liver disease or who are using medications that affect the CYP450 enzyme system (e.g., CYP2C19 and CYP3A4 substrates) should be cautious when using CBD, and make sure to inform their healthcare providers. Those using sedating medications should be careful with CBD, as some individuals experience sedation with the use of CBD. While CBD and other cannabinoids can increase or decrease serum levels of other medications, the role cannabinoids play with regard to herbal or other dietary supplements remains unclear.
Can CBD be used while pregnant or breastfeeding?	As there are currently no studies assessing the impact of CBD on individuals who are pregnant or breastfeeding, and the use of CBD products while pregnant or breastfeeding is strongly discouraged.
What are some of the biggest concerns and unknowns about CBD right now?	Some of the greatest unknowns about CBD include the effects of chronic CBD use, and how CBD may affect the developing brain of a fetus or an infant during pregnancy and/or breastfeeding, or the effects on the developing adolescent brain. There is also very limited information on how CBD interacts with dietary/herbal supplements or prescription drugs in humans, particularly since there are many variables such as route of administration (sublingual, vaping, capsule/pill, infused beverages, smoking, edibles, topical lotions/ointments), as well as different formulations (single extracted compound, plant-derived products) which can have a significant difference in their constituents. Another concern from animal studies is that CBD affects fertility, however whether this effect occurs in humans is unclear (Carvalho et al., 2020).
Why is CBD so difficult to study?	CBD may become easier to study now the Epidiolex is an FDA approved medication, if Epidiolex is the CBD product being used. However, testing commercial, non-FDA approved, legal hemp-based CBD products remains a challenge. It is of note that commercially available products, including full and broad-spectrum products, are not able to be studied via standard clinical trials at this time. This creates a discrepancy between the type of CBD being clinically used and the type of CBD being most likely used by patients. Additionally, there is an unusually high regulatory burden involved in clinical research on any cannabinoid, including CBD, when they are derived from cannabis (and not industrial hemp) given the Drug Enforcement Agency Schedule I status of cannabis. Gaining approval for administering Schedule I substances can be challenging and using federally approved cannabis products (such as the cannabis grown at the National Institute of Drug Abuse) may not offer the representative array of THC, CBD, or other cannabinoids that parallel those that are present in commercially available products.
Should clinicians recommend CBD for their patients?	Currently, there is not enough high-quality evidence to support the use of CBD as a treatment for any psychiatric symptom or disorder. Pending clinical trials will hopefully clarify its utility in treating psychotic and anxiety disorders, where it shows the most promise as a viable treatment option.