HHS Public Access

Author manuscript

*Psychopharmacology (Berl)*. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

*Psychopharmacology (Berl)*. 2021 January ; 238(1): 9–28. doi:10.1007/s00213-020-05712-8.

# Cannabidiol: Pharmacology and Therapeutic Targets

**Stevie C. Britch**[a,b], **Shanna Babalonis**[a,b], **Sharon L. Walsh**[a,b,c,d,e]

[a]Center on Drug and Alcohol Research, University of Kentucky, Lexington, KY 40508, USA

[b]Department of Behavioral Science, University of Kentucky, Lexington, KY 40508, USA

[c]Department of Pharmacology, University of Kentucky, Lexington, KY 40508, USA

[d]Department of Pharmaceutical Sciences, University of Kentucky, Lexington, KY 40508, USA

[e]Department of Psychiatry, University of Kentucky, Lexington, KY 40508, USA

## Abstract

Cannabidiol (CBD) products lacking regulatory approval are being used to self-treat a myriad of conditions and for its unsubstantiated health benefits. The scientific evidence supporting these claims largely arises not from controlled clinical trials, but from the recognition that CBD has numerous biological targets. Yet, CBD is commonly consumed and often in over-the-counter products that are unapproved and of unknown composition. Epidiolex® is the only product that has undergone rigorous pharmacokinetic assessment and testing in clinical trials; it was approved as a non-scheduled drug by the U.S. Food and Drug Administration for the treatment of intractable childhood-onset seizures. However, studies investigating CBD for other medical conditions are limited in number and often lack the scientific rigor, controls, or sample sizes required to draw clinically meaningful conclusions. Although Epidiolex® is safe for human consumption, recent changes in regulation of commercially available CBD products has resulted in limited quality control and products marketed with unknown CBD bioavailability. Even scientifically rigorous studies have used different sources of CBD and different suspension vehicles for administration, making it difficult to compare results among studies and resolve mixed outcomes. This paper reviews the molecular targets, pharmacokinetics, and safety and abuse liability of CBD; additionally, the extant evidence on its potential therapeutic effects for neurological disorders, pain, inflammation, conditions related to immune function, psychiatric disorders, and substance use are described.

### Keywords

Cannabidiol; Cannabis; Human; Pharmacokinetics; Medical cannabis; Marijuana



Corresponding Author: Stevie C. Britch, Mailing Address: 845 Angliana Ave, Lexington, KY 40508, Stevie.Britch@uky.edu, Phone: +1 (859) 562-2471, Fax: +1 (859) 257-5232.



Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

## Introduction

The phytocannabinoid cannabidiol (CBD) is a 21-carbon terpenophenolic compound with numerous molecular targets. Evidence that CBD has therapeutic promise largely stems from preclinical cellular and rodent studies, which suggest that CBD could be neuroprotective, cardioprotective, and anti-inflammatory. However, few highly controlled clinical trials investigating CBD have been conducted to elucidate its therapeutic potential. Moreover, many studies have been conducted with CBD preparations that have no regulatory approval. Epidiolex® (GW Pharmaceuticals) is the only marketed CBD monotherapy with U.S. Food and Drug Administration (FDA) approval. This review discusses CBD's molecular targets, its pharmacokinetic profile, evaluates its therapeutic potential, and highlights concerns regarding unregulated over-the-counter products. Only human studies (e.g., clinical trials and laboratory studies) investigating CBD alone (across various preparations and routes of administration [e.g., oral, inhaled/vaporized, topical, and sublingual]) are included; reports on nabiximols, such as Sativex® or cannabis material containing THC, are generally excluded. Additionally, review of the therapeutic evidence focuses largely on controlled clinical trials. See Pisanti et al. (2017) for a thorough review of the preclinical literature.

## Evidence for CBD Molecular Targets

The two primary cannabinoid receptors [cannabinoid 1 (CB1) and cannabinoid 2 (CB2)] are $G_{i/o}$-coupled protein receptors. CB1 receptors are located throughout the central nervous system (Herkenham et al. 1991), but have also been found in cardiac, lung, small intestine, kidney, and liver tissues (Buchholz et al. 2017), and on immune cells (Galiegue et al. 1995). In contrast, CB2 receptors are primarily located on immune cells (Nunez et al. 2004), in the gastrointestinal tract (Galiazzo et al. 2018), and in low densities in the central nervous system (Van Sickle et al. 2005). Evidence suggests that CBD activity at cannabinoid receptors is limited. A systematic review concluded that CBD effects at CB1 receptors are primarily due to indirect effects (i.e., no direct interaction with the orthosteric CB1 receptor binding site) (McPartland et al. 2015). One proposed mechanism of indirect CBD action at CB1 receptors is negative allosteric modulation, which has been reported in several *in vitro* studies (Chung et al. 2019; Laprairie et al. 2015; Tham et al. 2019). CBD inhibition of fatty acid amide hydrolase (FAAH) with increased anandamide has also been reported (Bisogno et al. 2001; De Petrocellis et al. 2011) – this is another proposed indirect mechanism of action. However, another study reported CBD activation of FAAH (Massi et al. 2008), and these cross-study inconsistencies have been attributed to differences in *in vitro* physiological test environments (Bih et al. 2015). With regard to CB2 receptors, CBD was reported to act as a low affinity agonist in receptor binding preparations (for review see McPartland et al., 2015; McPartland et al. 2015). *In vivo* studies support a potential role for CB2 as both CBD-induced reductions in cocaine self-administration (Galaj et al. 2019) and CBD's anti-seizure effects (Vilela et al. 2017) were blocked by CB2 antagonist pretreatment.

Although direct effects of CBD on cannabinoid receptors appear limited, over 65 molecular targets for CBD have been identified, including transient receptor potential vanilloid (TRPV) channels and serotonin ($5\text{-}HT_{1A}$) receptors, which have the most supporting evidence (Bih et

al. 2015) and are at least partially responsible for CBD's pharmacodynamic effects (Campos et al. 2012; Li et al. 2020; Nichols and Kaplan 2020; Soares and Campos 2017). Multiple studies have demonstrated that CBD acts as a low-potency, full agonist at TRPV1 and causes rapid desensitization of TRPV1 (Bisogno et al. 2001; De Petrocellis et al. 2011; Iannotti et al. 2014; Iannotti et al. 2019; Ligresti et al. 2006) (but also see Qin et al. 2008). *In vivo* studies have reported blockade of CBD effects by TRPV1 antagonists, including reductions in cocaine self-administration (Galaj et al. 2019), anti-seizure effects (Vilela et al. 2017), decreases in heart rate (in anesthetized rodents) (Kossakowski et al. 2019), and anti-inflammatory effects (Couch et al. 2017; Petrosino et al. 2018). CBD has also been shown to activate other TRPV receptors, including TRPV2, TRPV3, and TRPV4 (De Petrocellis et al. 2011; Morelli et al. 2014; Nabissi et al. 2015; Nabissi et al. 2013; Qin et al. 2008). Together, these findings suggest a role for TRPV receptors, particularly TRPV1, in mediating several potential therapeutic effects of CBD, such as neuroprotection and anti-convulsant effects (Gray and Whalley 2020; Lazarini-Lopes et al. 2020), anti-psychotic effects (Campos et al. 2012), and immunomodulatory effects (Nichols and Kaplan 2020).

CBD is an agonist at 5-$HT_{1A}$ receptors both *in vitro* (Russo et al. 2005; Yang et al. 2010) and *in vivo* (Alves et al. 2010; Galaj et al. 2019; Gomes et al. 2013; Gomes et al. 2012; Gomes et al. 2011; Hartmann et al. 2019; Resstel et al. 2009; Sartim et al. 2016; Soares et al. 2010; Sonego et al. 2016; Zanelati et al. 2010). *In vivo*, the 5-$HT_{1A}$ antagonist WAY100635 blocked CBD-induced panicolytic effects (Soares et al. 2010), antidepressant-like effects (Sartim et al. 2016; Zanelati et al. 2010), reversal of haloperidol-induced catalepsy (Sonego et al. 2016), anti-aggression (Hartmann et al. 2019), reductions in cocaine self-administration (Galaj et al. 2019), and reductions in autonomic stress responses (Resstel et al. 2009). WAY100635 also blocked CBD-induced anxiolytic effects (Gomes et al. 2011), stress-associated cardiovascular effects (Gomes et al. 2013), fear-associated freezing behavior (Gomes et al. 2012), and changes in baroreflex activity (Alves et al. 2010) when CBD was microinjected into the bed nucleus of the stria terminalis. These rodent studies suggest that many of CBD's behavioral effects are due to actions at $5HT_{1A}$ and that CBD may potentially be therapeutic for certain psychiatric disorders (Campos et al. 2012; Schier et al. 2012; Soares and Campos 2017). While these preclinical findings are exciting, rigorous clinical trials of CBD for psychiatric disorders are needed.

While there is more evidence supporting a role for TRPV channels and 5-HT receptors in CBD's mechanism of action, there is an emerging literature suggesting a multitude of other potential targets, including, but not limited to, adenosine, G-coupled protein receptor (GPR) 55, GPR18, GPR119, proliferator-activated receptor alpha, and glycine receptors (Atalay et al. 2019). Due, in part, to the multiplicity of CBD molecular targets (for review see Bih et al. 2015; Lee et al. 2017), the speculation regarding its therapeutic potential has been broad and includes applications for pain, inflammation, and psychiatric disorders, among others. However, evidence in support of its efficacy for these conditions is quite limited and only the efficacy of Epidiolex® for the treatment of epilepsy has been rigorously tested in humans resulting in FDA approval (see Therapeutic Implications section below for a review of clinical trials).

## Pharmacokinetics

While numerous studies have investigated the pharmacokinetics of CBD-THC combinations (for review see Millar et al. 2018), few have examined CBD alone (Table 1). CBD pharmacokinetics have been investigated using oral (Birnbaum et al. 2019; Consroe et al. 1991a; Devinsky et al. 2018b; Haney et al. 2016; Schoedel et al. 2018; Taylor et al. 2019; Taylor et al. 2018; Wheless et al. 2019), sublingual (Guy and Flint 2004), intravenous, and smoked administration methods (Ohlsson et al. 1986) (Table 1) in humans; however, only four used Epidiolex® (Devinsky et al. 2018b; Schoedel et al. 2018; Taylor et al. 2019; Taylor et al. 2018), the only approved formulation with data ensuring consistent product concentration and stability.

Oral administration has been the primary route used in controlled human studies with doses ranging from 20 to 6000 mg. Across studies the mean time to maximum concentration ($T_{max}$) for oral administration is highly variable and ranges from 1 to 6.13 h post-ingestion. One study examined the pharmacokinetics of oral CBD in healthy adults; Taylor and colleagues found that a single administration of Epidiolex® had a $T_{max}$ range of 3–5 h (Taylor et al. 2018). In adult polydrug users (self-report of cannabinoid use in the past 12 weeks and lifetime exposure of other drug classes included opioids and stimulants in 80–90% of participants) the $T_{max}$ of Epidiolex® was similar to that of healthy adults, 4.07 to 5.11 h (Schoedel et al. 2018), and in regular cannabis users oral CBD had a $T_{max}$ of 3 h (Haney et al. 2016). Sublingual CBD (GW-3009–01) appears to have an earlier $T_{max}$ than oral administration ($T_{max}$= 2.17 h) (Guy and Flint 2004), although no studies have done a direct comparison.

Several controlled studies suggest that CBD produces a dose-dependent, but not dose-proportional peak concentration (i.e., maximum concentration; $C_{max}$). The $C_{max}$ of Epidiolex® was 292 and 782 ng/ml after 1500 and 6000 mg, respectively, in healthy adults (Taylor et al. 2018). Epidiolex® also produced a dose-dependent $C_{max}$ after both a single dose and repeated dosing in children with Dravet syndrome (Devinsky et al. 2018b). Similar findings were observed in children with treatment resistant epilepsy receiving an unlicensed CBD solution (Wheless et al. 2019) (Table 1). In contrast, in polydrug users the relationship between Epidiolex® dose and $C_{max}$ was *not* dose-dependent (Schoedel et al. 2018), and, in regular cannabis users, unlicensed CBD $C_{max}$ was highly variable ranging from 1.6–271.9 ng/ml after a single dose of 800 mg oral CBD (Haney et al. 2016). It is unclear if past or recent experience with cannabinoids or other psychoactive substances can alter CBD pharmacokinetics; as no studies have directly compared the pharmacokinetics of CBD between healthy adults and regular cannabis users or people who use multiple psychoactive substances. One additional study investigated excretion of CBD in urine after both oral and vaporized administration in healthy adults and found that oral CBD (100 mg) resulted in a higher urine $C_{max}$ than vaporized CBD-dominant plant material containing 100 mg CBD and 3.7 mg THC (776 and 261 ng/ml, respectively) (Spindle et al. 2020b).

Few studies have determined the half-life (t½) of CBD; after acute dosing it has been reported that Epidiolex® has a t½ of 14.39–16.61 h (Taylor et al. 2018), and between 21.6–33.5 h was reported for children with treatment-resistant epilepsy (Wheless et al. 2019). One

study in adult men with a history of cannabis reported a t½ of 24 and 31 h, respectively, for intravenous CBD (20 mg) smoked CBD (19 mg) (Ohlsson et al. 1986). After repeated CBD administration, a t½ of 68 h for oral CBD was reported in Huntington's patients (Consroe et al. 1991a). There is also emerging interest in CBD metabolites with at least one, 7-OH-CBD, reported to be an active metabolite (Taylor et al. 2019; Taylor et al. 2018; Wheless et al. 2019). Several studies have examined the pharmacokinetic profile of different metabolites and these findings are detailed in Table 2.

It has been shown that the presence of food (i.e., a high fat meal) can significantly increase CBD exposure (i.e., 1500 mg, p.o.), with a 4-fold increase in exposure (i.e., area-under-the curve; AUC) compared to fasting in healthy normal volunteers (Taylor et al. 2018). A study in adults with refractory epilepsy also reported a food-induced increase in CBD exposure (i.e., 300 mg, p.o.) that was even greater (i.e., 15-fold increase in AUC) (Birnbaum et al. 2019). CBD t½ was also modified by food-intake from 30.33 h to 24.4 h (~20%) in the fasted versus fed condition in healthy adults receiving Epidiolex® (Taylor et al. 2018) and from 39 h to 24.3 (38%) in adults with refractory epilepsy (Birnbaum et al. 2019). It should also be noted that patients with hepatic impairment may require adjustment of their CBD dose; in one study AUC increased with severity of hepatic impairment, and those with severe impairment had a roughly 5-fold increased AUC (Table 1; Taylor et al. 2019).

Additionally, drug-drug interactions may result in changes in the pharmacokinetic effects of both CBD and other drugs. Documentation of drug-drug interactions with CBD have been reported in recent publications (Brown and Winterstein 2019; Fitzcharles et al. 2020). CBD acts as an inhibitor or inducer of several cytochrome P450 isoforms including 3A4, 2C19, 2C8, 2C9, 2D6, 1A2 and 2B6, and has minor activity at several others. (Highlights of Prescribing Information 2018; Stout and Cimino 2014). As CYP450 enzymes are involved in metabolism of the majority of pharmacotherapies (Zanger and Schwab 2013), CBD has the potential to cause interaction effects with many over-the-counter and prescription medications. For example, in a pediatric expanded-access study, 13 participants taking clobazam (anti-seizure treatment) also received oral CBD (titrated up to 20 mg/kg/day) for 4 weeks – concomitant CBD administration resulted in a 60% increase in serum clobazam and a 500% increase in the metabolite norclobazam (Geffrey et al. 2015). Two pediatric case reports identified drug-drug interactions with other pharmacological agents: 1) CBD was implicated in a 4-fold increase in serum concentrations of everolimus (an antineoplastic chemotherapeutic also used for seizure management) – the authors suggest that this was likely mediated through a CYP 3A4 interaction (Wiemer-Kruel et al. 2019); 2) one patient taking methadone experienced increased fatigue and somnolence and over a 2-fold increase in serum methadone concentrations after initiating CBD - these effects resolved upon removal of CBD (Madden et al. 2020). Additionally warnings in the Epidiolex® package insert suggest that when given in combination with the anticonvulsant valproate, liver enzymes can become elevated (Highlights of Prescribing Information 2018) Overall, the potential for drug-drug interaction should be considered when starting treatment on CBD treatment.

## Safety and Abuse Liability

The World Health Organization's report on CBD concluded that it has a good safety profile with limited side effects (Cannabidiol (CBD) Critical Review Report 2018). Several controlled human laboratory studies of oral (200–800 mg) and sublingual (20 mg) CBD reported limited effects on physiological outcomes, including heart rate and blood pressure (Babalonis et al. 2017; Guy and Flint 2004; Haney et al. 2016; Martin-Santos et al. 2012; Schoedel et al. 2018; Taylor et al. 2018). In contrast, two recent randomized, double-blind, placebo-controlled studies found a modest decrease in arterial pressure and systolic blood pressure after acute CBD administration (Jadoon et al. 2017; Sultan et al. 2020), but this effect dissipated when CBD was administered daily for 7 days (Sultan et al. 2020). The registration studies for Epidiolex® reported the most common side effects as diarrhea, headache, decreased appetite, and somnolence (Devinsky et al. 2014; Devinsky et al. 2017; Devinsky et al. 2016; Devinsky et al. 2018a; Devinsky et al. 2018b; Schoedel et al. 2018; Szaflarski et al. 2018; Taylor et al. 2018). Interestingly, a recent meta-analysis reported, in children with epilepsy, that CBD was associated with higher rates of pneumonia compared to placebo and that high doses of CBD (≥20 mg/kg) were associated with abnormal liver function tests (Chesney et al. 2020).

With regard to abuse liability, the vast majority of studies evaluating acute dosing concluded that there is no signal for abuse potential with CBD (Babalonis et al. 2017; Haney et al. 2016; Martin-Santos et al. 2012; Schoedel et al. 2018). This is consistent with the re-scheduling of Epidiolex® as a non-scheduled drug in the U.S. (Highlights of Prescribing Information 2018). The exceptions to this body of evidence include two randomized, double-blind, placebo-controlled studies: one examined vaporized CBD (100 mg) and reported increased ratings of "Pleasant Drug Effect" and "Like Drug Effect" (Spindle et al. 2020a) while another reported that vaporized CBD (400 mg) increased subjective ratings of intoxication on a visual analog scale (Solowij et al. 2019).

Of critical importance, the majority of CBD products being sold have not been approved by the FDA. Unregulated CBD is available in numerous formulations, including oral capsules or tinctures; sublingual oils; topical creams, balms, and salves; e-liquids or crystalized formations (wax) for vaporization; and dietary supplement forms. These products are sold online and in retail shops with advertising suggesting a vast array of unsubstantiated medical and psychiatric benefits, and to improve beauty, hygiene, and nutrition. Estimated sales of these products were between 600 million and 2 billion USD in 2018, and investment companies predict sales will reach 16 billion USD by 2025 (Azer et al. 2019). Whether or not these unregulated products contain CBD as advertised is unknown, and unsanctioned CBD products may contain hazardous chemicals (Bonn-Miller et al. 2017; FDA 2019; FDA 2020b; Poklis et al. 2019). Analysis of 48 products purchased online found that only 31% were accurately labeled in regard to CBD concentration and 21% contained THC (Bonn-Miller et al. 2017). Similarly, a study in the United Kingdom reported only 38% of over-the-counter products contained ±10% of the advertised quantity and 55% contained THC (Liebling et al. 2020). The FDA reported similar findings with inconsistent CBD concentrations and the presence of THC (FDA 2019). The FDA has sent a myriad of warning letters due to inaccurate labeling and false health claims, including, but not limited

to, treatment for chronic pain, anxiety, and opioid use disorder (FDA 2019; FDA 2020b). Contamination with 5-fluoro MDMB-PINACA and dextromethorphan has also been reported (Poklis et al. 2019). CBD product contamination could lead to unanticipated psychoactive effects and positive urine drug screens in the case of THC. Several states with medical cannabis laws require laboratory testing of products, but uniform testing protocols have not been developed (e.g., array of tests conducted, assay technology, sensitivity parameters). There have been no systematic evaluations to determine the accuracy of laboratory reports, product labels, or product contamination rates of products available in the state-sponsored dispensaries and those sold elsewhere (i.e., online, unregulated retail shops) (Corroon et al. 2020).

There has been concern that oral CBD could transform into THC in the human gut, but this hypothesis has recently been refuted by empirical studies confirming that CBD does *not* transform to THC in humans, even at high doses (4500 mg acute oral dose; Crippa et al. 2019; Schoedel et al. 2018; Spindle et al. 2020b). Thus, intoxication or THC positive drug screens associated with CBD products are thought to be due to contamination.

## Therapeutic Implications

### Neurological Disorders

The most compelling evidence supporting the medicinal use of CBD is for the treatment of epilepsy (Table 3). An early study suggesting a benefit of CBD for seizure disorders was a very small (n=15) randomized, double-blind, placebo-controlled study of patients with secondary generalized epilepsy (Cunha et al. 1980). CBD (200–300 mg, p.o./daily for up to 18 weeks) was associated with reduced seizure episodes on a monthly seizure scale of 0–3. Open-label and expanded access studies with limited rigor have also examined CBD in patients with childhood onset seizures and febrile infection-related epilepsy (Devinsky et al. 2016; Gofshteyn et al. 2017; Szaflarski et al. 2018). An open-label trial of 137 patients (ages 1–30) with childhood onset seizures described as “severe, intractable, [and] treatment-resistant” explored oral CBD (up to 50 mg/kg/day) and reported a 36.5% reduction of median monthly seizures (Devinsky et al. 2016). In a similar open-label add-on study, adults and children with various types of epilepsy received 12–48 weeks of treatment with Epidiolex® (up to 50 mg/kg/day); after 12 weeks of treatment, Chalfont Seizure Severity Scores decreased by 51.3% (Szaflarski et al. 2018).

Rigorous studies have recently established CBD (Epidiolex®) as an effective treatment for Dravet and Lennox-Gastaut syndromes, and more recently seizures that are secondary to tuberous sclerosis complex, all forms of childhood epilepsy associated with severe, intractable seizures (Table 3). A randomized, double-blind trial of 120 patients ages 2–18, with Dravet Syndrome found that 20 mg/kg/day oral CBD for 14 weeks decreased median monthly motor seizures by 38.9% compared to 13.3% with placebo (Devinsky et al. 2017). Two double-blind randomized studies examined CBD for Lennox-Gastaut. In the first, patients (n=212; ages 2–55) who received 10 or 20 mg/kg/day oral CBD had a 37.2% and 41.9% decrease in drop-seizure activity from baseline, respectively, compared to a 17.2% decrease in patients who received placebo (Devinsky et al. 2018a). In the second, patients with treatment-resistant Lennox-Gastaut (n=171; ages 2–55) received 20 mg/kg/day oral

CBD or placebo for 14 weeks. Those receiving CBD had a 43.9% reduction in drop-seizures, compared to a 21.8% decrease in patients who received placebo (Thiele et al. 2018). These studies provided the supportive evidence of efficacy and safety for CBD for Dravet and Lennox-Gastaut syndromes leading to its approval by the FDA in 2018. In July 2020 the FDA expanded Epidiolex® approval to include treatment of seizures due to tuberous sclerosis complex (FDA 2020a). An initial open-label add on study reported that 3 months of treatment with Epidiolex® titrated up to 50 mg/kg/day decreased median weekly seizures by 48.8% (Hess et al. 2016). The FDA reported that in a randomized, double blind, placebo-controlled trial of 224 patients, Epidiolex® decreased seizure frequency after 8 weeks of treatment (FDA 2020a).

CBD has been investigated in other neurological conditions, including Huntington's and Parkinson's disease (Table 3). A small randomized, double-blind, placebo-controlled, crossover study of 15 patients with mild to moderate Huntington's disease received 10 mg/kg/day oral CBD (Consroe et al. 1991b). Patients who received CBD had no improvement of Huntington's disease-related symptoms (e.g., chorea, tongue extension) and no benefit of CBD was found by physician nor patient assessment (Consroe et al. 1991b). Two studies have explored CBD for the treatment of Parkinson's disease. A small, open-label pilot study (n=6) suggested that oral CBD (starting at 150 mg/day and increasing weekly for 4 weeks) might improve Parkinson's-related psychotic symptoms (Zuardi et al. 2009). In a subsequent, randomized, double-blind study by the same group, 21 patients with Parkinson's disease received 75 or 300 mg oral CBD or placebo daily for 6 weeks (Chagas et al. 2014). Patients who received CBD scored similar to those who received placebo on the Unified Parkinson's Disease Rating Scale (a measure of Parkinson's disease severity), but patients who received 300 mg CBD had better scores on the Parkinson's Disease Questionnaire compared to those who received placebo (Chagas et al. 2014). The results of these two small trials are promising; however, larger randomized controlled trials are needed to determine the efficacy of CBD for the treatment of Parkinson's disease. For a review of CBD effects on neurological disorders in animal models see Elsaid et al. (2019).

## Pain, Inflammation, and Immune Function

A limited number of studies of varying rigor have investigated CBD for efficacy in pain conditions, including multiple sclerosis, fibromyalgia, Crohn's disease, and neuropathic pain (Table 4). In a randomized, double-blind, placebo-controlled, crossover study 20 patients with multiple sclerosis, spinal injury, brachial plexus lesions, or amputation received CBD (2.5–120 mg/day of sublingual spray) treatment which decreased pain on a visual analog scale, but did not improve other symptoms such as spasms, coordination, bladder control, or emotional well-being (Wade et al. 2003). In contrast, a randomized, double-blind, placebo-controlled, crossover study in which 34 patients with chronic pain primarily due to multiple sclerosis received a relatively low dose (2.5 mg) of sublingual CBD spray daily for 8 weeks found little-to-no pain improvement (Notcutt et al. 2004). Other studies using low doses also found that CBD was not analgesic: in a randomized, double-blind, placebo-controlled, crossover study of 20 patients with chronic pain due to fibromyalgia, vaporized (inhaled) Bedrolite (18.4 mg CBD & < 1 mg THC) did not improve experimental pressure or electrical pain (van de Donk et al. 2019) and sublingual CBD (20 mg/day for 8 weeks) did

not alter the Crohn's disease activity index – a global measure of Crohn's disease severity that includes pain – compared to placebo in a randomized, double-blind study of 19 patients (Naftali et al. 2017). Collectively these studies suggest that CBD is not an effective analgesic, but they are limited by a low dose of CBD. One exploratory study reported that 50 out of 94 patients on opioids for chronic pain who were treated with CBD-rich hemp extract (self-titrated to ~30 mg/day, p.o.) reduced their opioid intake (Capano et al. 2020). In a larger randomized, double-blind study, patients with peripheral neuropathy of various etiologies (n=29) received topical CBD (250 mg/3 fl. oz.) up to 4 times daily for 4 weeks or placebo, after 4 weeks of treatment the placebo group crossed-over to receiving CBD and all participants were treated for an additional 4 weeks (Xu et al. 2020). This study reported a larger decrease in "intense, sharp, cold, and itchy" on the Neuropathic Pain Scale in the CBD group compared to placebo. While this study is intriguing, further studies are required to confirm that CBD is an efficacious analgesic when applied topically.

There are also a multitude of conditions related to inflammation and immune function for which a single randomized controlled study has reported on the effects of CBD, including gastrointestinal inflammation, ulcerative colitis, ocular hypertension and glaucoma, graft-versus-host disease, and diabetes (Table 4). First, in a randomized, double-blind, placebo-controlled study 38 male participants received aspirin to increase gastrointestinal absorption of lactulose and mannitol and this effect was reduced in participants who received CBD (600 mg, p.o.) (Couch et al. 2019), suggesting CBD may decrease gastrointestinal inflammation. However, a randomized, double-blind, placebo-controlled, pilot study (n=6) found that CBD-rich extract did not improve remission rates in patients with ulcerative colitis (Irving et al. 2018). In a randomized, double-blind, placebo-controlled, crossover, pilot study, patients (n=6) with ocular hypertension or glaucoma received sublingual CBD (20 and 40 mg). Intraocular pressure did not change when patients received 20 mg CBD, but *increased* when they received 40 mg, suggesting CBD may worsen ocular-related disease (Tomida et al. 2006). A phase II clinical trial of 48 patients who received oral CBD solution (300 mg/day) in addition to prophylactic immunosuppressive treatment for the prevention graft-versus-host-disease due to allogeneic hematopoietic cell transplantation suggested CBD may decrease rates of graft-versus-hostdisease when compared to a historical control of 101 patients (Yeshurun et al. 2015). Lastly, in a randomized, double-blind, placebo-controlled study of 62 patients with type II diabetes, CBD (200 mg/day) produced minimal effects on glycemic control (Jadoon et al. 2016). While these reports from well controlled studies are intriguing, there is insufficient evidence to draw clinically meaningful conclusions. For a review of preclinical findings on CBD effects on pain and inflammation see Burstein (2015).

## Psychiatric Disorders and Substance Use

Numerous studies of varying rigor have examined CBD for its anxiolytic effects (Table 5). This body of work is difficult to interpret because studies test different doses, several limit enrollment to men, and some enroll patients with anxiety disorders while others employ experimental anxiety paradigms. A small (n=10), randomized, double-blind, placebo-controlled, crossover study in men with generalized anxiety reported that CBD (400 mg, p.o.) reduced subjective anxiety on a visual analog mood scale (Crippa et al. 2011). A double-blind study of healthy adults (n=40) reported that CBD (300 mg, p.o.) decreased

anxiety after a simulated public speaking test compared to placebo (and similar to other anxiolytics) (Zuardi et al. 1993). CBD 300 mg, p.o., but not 100 or 900 mg, also reduced subjective ratings of anxiety during a test of experimentally induced public speaking in a randomized, double-blind, placebo-controlled study (n=60) (Zuardi et al. 2017). Similarly, a randomized, double-blind, placebo-controlled study (n=57) in men reported that 300 mg oral CBD, but not 150 or 600 mg, decreased anxiety during a simulated public speaking test (Linares et al. 2019). In a randomized, double-blind, placebo-controlled, crossover study (n=16) CBD (600 mg, p.o.) was not anxiolytic (Martin-Santos et al. 2012). CBD (600 mg, p.o.) was also not anxiolytic in a randomized, double-blind, placebo-controlled study of 32 participants with high trait paranoia and persecutory ideation (Hundal et al. 2018). In two double-blind, placebo-controlled, within-subjects studies (n=15/study) CBD (600 mg, p.o.) did not reduce subjective ratings of anxiety on a visual analog mood scale or the Spielberger State Trait Anxiety Inventory (Borgwardt et al. 2008; Fusar-Poli et al. 2009). However, one study found that 600 mg oral CBD was anxiolytic in a randomized, double-blind, placebo-controlled study of 36 undergraduate students with social phobia (Bergamaschi et al. 2011). In regard to repeated CBD administration, in one randomized, double-blind study, patients (n=58) with a clinically high risk for psychosis received 600 mg CBD (p.o.) daily for 1 week (Appiah-Kusi et al. 2020). There was no significant difference between participants who received CBD versus placebo on the Tier Social Stress Test. Overall, these mixed results suggest that controlled studies to identify an effective dose range and dosing regimen (acute, repeated dosing) are needed, particularly in individuals with anxiety disorders. Despite this lack of controlled data, over the counter CBD products are being advertised as beneficial for such conditions. For review of pre-clinical studies examining CBD anxiolysis see Blessing et al. (2015).

In regard to other psychiatric disorders, a randomized, double-blind study in 33 patients reported that CBD (200–800 mg/daily) improved clinical symptoms of schizophrenia compared to baseline and similar to the antipsychotic amisulpride (Leweke et al. 2012). Another randomized, double-blind, placebo-controlled clinical trial in 88 patients with schizophrenia found oral CBD solution (1000 mg/day for 6 weeks) decreased positive psychotic symptoms (McGuire et al. 2018). Yet, CBD (600 mg/day, p.o.) did *not* improve psychotic symptoms in a randomized, double-blind, placebo-controlled study of 36 patients with schizophrenia (Boggs et al. 2018). Additionally, CBD (300 and 600 mg, p.o.) did not alter scores on the Positive and Negative Symptoms Scale or the Brief Psychiatric Rating Scale and did not change performance on the Stroop Color Word Test in a double-blind, placebo-controlled study of 28 patients with schizophrenia (Hallak et al. 2010). For a review of CBD effects on psychiatric disorders in animal models see Elsaid et al. (2019).

Although it is unclear if CBD can reduce psychiatric illness, it may reduce psychotic symptoms associated with THC usage (Table 5). In a double-blind, placebo-controlled, crossover study, CBD (5 mg, I.V.) prevented the acute psychotic symptoms of THC (1.25 mg, I.V.) in three out of three men that experienced THC-induced psychosis (Bhattacharyya et al. 2010). Similarly, oral CBD (600 mg) prevented THC (1.5 mg I.V.) -induced paranoia in a randomized, double-blind, placebo-controlled study (n=22) (Englund et al. 2013). Vaporized CBD (16 mg) inhibited THC (8 mg, vaporized) -induced increases on the Psychomimetic State Inventory in a randomized, double-blind, placebo-controlled study of

light cannabis users (n=24) (Morgan et al. 2018). CBD may also alter THC intoxication, although results from these studies are inconsistent, possibly due to differences in CBD formulation and/or route of administration. In an early, double-blind, placebo-controlled study (n=40) oral CBD (15–60 mg) inhibited THC's subjective effects (Karniol et al. 1974). In a randomized, double-blind study (n=36) vaporized CBD-THC combinations with relatively high CBD (400 mg) were less intoxicating than THC alone (8 mg), however, when the CBD dose was reduced to 4 mg it increased THC-induced intoxication (Solowij et al. 2019). Another randomized, double-blind, placebo-controlled, crossover study in 31 cannabis smokers found that CBD (200–800 mg, p.o.) did not change the subjective intoxicating effects of smoked cannabis containing THC (5.08–5.30%), nor did it alter cannabis self-administration (Haney et al. 2016). In a randomized, double-blind, placebo-controlled, within-subjects study participants (n=14) reported no subjective difference in drug effect between vaporized CBD+THC (11% CBD, 11% THC) and THC only (<1%CBD, 11%THC) (Arkell et al. 2019).

Despite popular belief, few human studies examining CBD treatment of substance use have been conducted and while some of these results are intriguing, not enough evidence exists to indicate CBD as a viable treatment option for substance use disorders (Table 5). Inhaled CBD decreased tobacco smoking by 40% in a randomized, double-blind, placebo-controlled study of 24 participants who wanted to quit smoking (Morgan et al. 2013). In a randomized, double-blind, placebo-controlled, crossover study of 33 non-treatment seeking smokers undergoing short-term tobacco abstinence, CBD (800 mg, p.o.) decreased attention bias toward cigarette cues, but did not alter craving or withdrawal ratings (Hindocha et al. 2018). In a randomized, double-blind, placebo-controlled, crossover study (n=10), CBD (200 mg, p.o.) decreased blood alcohol levels, but did not alter the behavioral effects of alcohol (Consroe et al. 1979). For a review of CBD effects on alcohol consumption in animal models see Turna et al. (2019). Regarding opioids, one double-blind, placebo-controlled, crossover study (n=17) reported that CBD (400 or 800 mg, p.o.) did not alter pharmacokinetics or adverse effects of I.V. fentanyl (Manini et al. 2015). Another randomized, double-blind, placebo-controlled study of participants (n=42) with heroin use disorder who were abstinent reported that Epidiolex® (400 or 800 mg) inhibited drug-cue induced craving and anxiety, but not heroin craving (Hurd et al. 2019). While these studies are intriguing, they do not provide substantive data to draw clinically meaningful conclusions.

## Conclusions

CBD has diverse molecular targets, including indirect activity at cannabinoid receptors and agonism of TRPV and 5-$HT_{1A}$, and additional molecular targets are being investigated (Bih et al. 2015). This array of targets has resulted in claims that CBD is efficacious for a myriad of health conditions, but clinical data supporting CBD as a pharmacotherapy are limited to the anti-epileptic effects of Epidiolex®. Epidiolex® has been developed to produce accurate biological exposure and has undergone rigorous pharmacokinetic evaluations (Devinsky et al. 2018b; Schoedel et al. 2018; Taylor et al. 2019; Taylor et al. 2018). However, six studies have characterized the pharmacokinetic effects of other formulations of CBD, including oral preparations (Birnbaum et al. 2019; Consroe et al. 1991a; Haney et al. 2016; Wheless et al.

2019), sublingual CBD (Guy and Flint 2004), and smoked CBD (Ohlsson et al. 1986). There are variations in the reported pharmacokinetic profiles across these studies that may be attributable to the formulation, the chosen study sample (i.e. drug use history), drug-drug interactions (i.e., concomitant seizure medication), and other factors (e.g., food intake with high fat content).

While the consensus is that pharmaceutical-grade CBD has a favorable safety profile with limited side effects (Cannabidiol (CBD) Critical Review Report 2018), this may not generalize across all populations (children, elderly) (Chesney et al. 2020) or across all CBD formulations, as unregulated retail products carry inaccurate labels and have the potential to be contaminated with hazardous chemicals (Bonn-Miller et al. 2017; Corroon et al. 2020; FDA 2019; FDA 2020b; Poklis et al. 2019).

The FDA has approved the use of Epidiolex® for the treatment of seizures associated with Dravet Syndrome, Lennox-Gastaut Syndrome, and tuberous sclerosis complex. Clinical trials investigating the efficacy of CBD for the treatment of pain, autoimmune diseases, psychiatric disorders, substance use, and various other conditions often rely on a single acute dose, but effective doses may vary across disease states. Clinical trials with multiple doses given repeatedly for extended periods of time are needed before CBD can be recommended as a viable pharmacotherapy for these conditions. However, patients are self-treating with over-the-counter, untested CBD products for numerous psychiatric and medical conditions. The lack of evidence supporting the efficacy of CBD for these conditions and the absence of consistent manufacturing quality-control with these unapproved CBD products warrants concern for public health and patient safety.

## Acknowledgements and Disclosers:

This work was supported by National Institute on Drug Abuse grants R21 DA045101 and R01 DA045700 (Dr. Babalonis); R01 DA016718 and R01 DA040637 (Dr. Walsh); and T32 DA035200 (Dr. Britch). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors have no conflicts of interest to disclose.

## References

Alves FH, Crestani CC, Gomes FV, Guimaraes FS, Correa FM, Resstel LB (2010) Cannabidiol injected into the bed nucleus of the stria terminalis modulates baroreflex activity through 5-HT1A receptors Pharmacological research 62:228–236 doi:10.1016/j.phrs.2010.05.003 [PubMed: 20621717]

Appiah-Kusi E et al. (2020) Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis Psychopharmacology 237:1121–1130 doi:10.1007/s00213-019-05442-6 [PubMed: 31915861]

Arkell TR et al. (2019) Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition Psychopharmacology (Berl) 236:2713–2724 doi:10.1007/s00213-019-05246-8 [PubMed: 31044290]

Atalay S, Jarocka-Karpowicz I, Skrzydlewska E (2019) Antioxidative and Anti-Inflammatory Properties of Cannabidiol Antioxidants (Basel) 9 doi:10.3390/antiox9010021

Azer V et al. (2019) Cowen's Collective View of CBD. https://www.cowen.com/insights/cowen-collective-view-of-cbd/.

Babalonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S, Walsh SL (2017) Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers Drug Alcohol Depend 172:9–13 doi:10.1016/j.drugalcdep.2016.11.030 [PubMed: 28088032]

Bergamaschi MM et al. (2011) Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients Neuropsychopharmacology 36:1219–1226 doi:10.1038/npp.2011.6 [PubMed: 21307846]

Bhattacharyya S et al. (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology Neuropsychopharmacology 35:764–774 doi:10.1038/npp.2009.184 [PubMed: 19924114]

Bih IC, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ (2015) Molecular Targets of Cannabidiol in Neurological Disorders Neurotherapeutics 12:699–730 doi:10.1007/s13311-015-0377-3 [PubMed: 26264914]

Birnbaum AK et al. (2019) Food effect on pharmacokinetics of cannabidiol oral capsules in adult patients with refractory epilepsy Epilepsia 60:1586–1592 doi:10.1111/epi.16093 [PubMed: 31247132]

Bisogno T et al. (2001) Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide Br J Pharmacol 134:845–852 doi:10.1038/sj.bjp.0704327 [PubMed: 11606325]

Blessing EM, Steenkamp MM, Manzanares J, Marmar CR (2015) Cannabidiol as a Potential Treatment for Anxiety Disorders Neurotherapeutics 12:825–836 doi:10.1007/s13311-015-0387-1 [PubMed: 26341731]

Boggs DL et al. (2018) The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial Psychopharmacology (Berl) 235:1923–1932 doi:10.1007/s00213-018-4885-9 [PubMed: 29619533]

Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R (2017) Labeling Accuracy of Cannabidiol Extracts Sold Online Jama 318:1708–1709 doi:10.1001/jama.2017.11909 [PubMed: 29114823]

Borgwardt SJ et al. (2008) Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition Biol Psychiatry 64:966–973 doi:10.1016/j.biopsych.2008.05.011 [PubMed: 18589404]

Brown JD, Winterstein AG (2019) Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use J Clin Med 8 doi:10.3390/jcm8070989

Buchholz HG et al. (2017) Whole-body biodistribution of the cannabinoid type 1 receptor ligand [(18)F]MK-9470 in the rat Nucl Med Biol 52:63–69 doi:10.1016/j.nucmedbio.2017.06.003 [PubMed: 28648984]

Burstein S (2015) Cannabidiol (CBD) and its analogs: a review of their effects on inflammation Bioorg Med Chem 23:1377–1385 doi:10.1016/j.bmc.2015.01.059 [PubMed: 25703248]

Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimarães FS (2012) Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders Philos Trans R Soc Lond B Biol Sci 367:3364–3378 doi:10.1098/rstb.2011.0389 [PubMed: 23108553]

Cannabidiol (CBD) Critical Review Report (2018). World Health Organization, Expert Committee on Drug Dependence, Geneva

Capano A, Weaver R, Burkman E (2020) Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study Postgrad Med 132:56–61 doi:10.1080/00325481.2019.1685298 [PubMed: 31711352]

Chagas MH et al. (2014) Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial Journal of psychopharmacology (Oxford, England) 28:1088–1098 doi:10.1177/0269881114550355

Chesney E et al. (2020) Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials Neuropsychopharmacology doi:10.1038/s41386-020-0667-2

Chung H, Fierro A, Pessoa-Mahana CD (2019) Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: An In Silico study PloS one 14:e0220025 doi:10.1371/journal.pone.0220025 [PubMed: 31335889]

Consroe P, Carlini EA, Zwicker AP, Lacerda LA (1979) Interaction of cannabidiol and alcohol in humans Psychopharmacology (Berl) 66:45–50 doi:10.1007/bf00431988 [PubMed: 120541]

Consroe P, Kennedy K, Schram K (1991a) Assay of plasma cannabidiol by capillary gas chromatography/ion trap mass spectroscopy following high-dose repeated daily oral administration in humans Pharmacology Biochemistry and Behavior 40:517–522 doi:10.1016/0091-3057(91)90357-8

Consroe P et al. (1991b) Controlled clinical trial of cannabidiol in Huntington's disease Pharmacol Biochem Behav 40:701–708 doi:10.1016/0091-3057(91)90386-g [PubMed: 1839644]

Corroon J, MacKay D, Dolphin W (2020) Labeling of Cannabidiol Products: A Public Health Perspective Cannabis and Cannabinoid Research doi:10.1089/can.2019.0101

Couch DG, Cook H, Ortori C, Barrett D, Lund JN, O'Sullivan SE (2019) Palmitoylethanolamide and Cannabidiol Prevent Inflammation-induced Hyperpermeability of the Human Gut In Vitro and In Vivo—A Randomized, Placebo-controlled, Double-blind Controlled Trial Inflammatory Bowel Diseases 25:1006–1018 [PubMed: 31054246]

Couch DG, Tasker C, Theophilidou E, Lund JN, O'Sullivan SE (2017) Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon Clin Sci (Lond) 131:2611–2626 doi:10.1042/cs20171288 [PubMed: 28954820]

Crippa JA et al. (2011) Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report Journal of psychopharmacology (Oxford, England) 25:121–130 doi:10.1177/0269881110379283

Crippa JAS et al. (2019) Oral Cannabidiol Does Not Convert to Δ8-THC or Δ9-THC in Humans: A Pharmacokinetic Study in Healthy Subjects Cannabis and Cannabinoid Research 0:null doi:10.1089/can.2019.0024

Cunha JM et al. (1980) Chronic administration of cannabidiol to healthy volunteers and epileptic patients Pharmacology 21:175–185 doi:10.1159/000137430 [PubMed: 7413719]

De Petrocellis L et al. (2011) Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes Br J Pharmacol 163:1479–1494 doi:10.1111/j.1476-5381.2010.01166.x [PubMed: 21175579]

Devinsky O et al. (2014) Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders Epilepsia 55:791–802 doi:10.1111/epi.12631 [PubMed: 24854329]

Devinsky O et al. (2017) Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome N Engl J Med 376:2011–2020 doi:10.1056/NEJMoa1611618 [PubMed: 28538134]

Devinsky O et al. (2016) Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial Lancet Neurol 15:270–278 doi:10.1016/s1474-4422(15)00379-8 [PubMed: 26724101]

Devinsky O et al. (2018a) Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome N Engl J Med 378:1888–1897 doi:10.1056/NEJMoa1714631 [PubMed: 29768152]

Devinsky O et al. (2018b) Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome Neurology 90:e1204–e1211 doi:10.1212/wnl.0000000000005254 [PubMed: 29540584]

Elsaid S, Kloiber S, Le Foll B (2019) Effects of cannabidiol (CBD) in neuropsychiatric disorders: A review of pre-clinical and clinical findings Prog Mol Biol Transl Sci 167:25–75 doi:10.1016/bs.pmbts.2019.06.005 [PubMed: 31601406]

Englund A et al. (2013) Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment Journal of psychopharmacology (Oxford, England) 27:19–27 doi:10.1177/0269881112460109

FDA (2019) Warning Letters and Test Results for Cannabidiol-Related Products.

FDA (2020a) FDA Approves New Indication for Drug Containing an Active Ingredient Derived from Cannabis to Treat Seizures in Rare Genetic Disease.

FDA (2020b) FDA Warns Companies Illegally Selling CBD Products to Treat Medical Conditions, Opioid Addiction.

Fitzcharles MA, Clauw DJ, Hauser W (2020) A cautious hope for cannabidiol (CBD) in rheumatology care Arthritis Care Res (Hoboken) doi:10.1002/acr.24176

Fusar-Poli P et al. (2009) Distinct Effects of Δ9-Tetrahydrocannabinol and Cannabidiol on Neural Activation During Emotional Processing Archives of General Psychiatry 66:95–105 doi:10.1001/archgenpsychiatry.2008.519 [PubMed: 19124693]

Galaj E, Bi GH, Yang HJ, Xi ZX (2019) Cannabidiol attenuates the rewarding effects of cocaine in rats by CB2, 5-TH1A and TRPV1 receptor mechanisms Neuropharmacology:107740 doi:10.1016/j.neuropharm.2019.107740 [PubMed: 31437433]

Galiazzo G et al. (2018) Localization of cannabinoid receptors CB1, CB2, GPR55, and PPARalpha in the canine gastrointestinal tract Histochem Cell Biol 150:187–205 doi:10.1007/s00418-018-1684-7 [PubMed: 29882158]

Galiegue S et al. (1995) Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations European journal of biochemistry 232:54–61 [PubMed: 7556170]

Geffrey AL, Pollack SF, Bruno PL, Thiele EA (2015) Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy Epilepsia 56:1246–1251 doi:10.1111/epi.13060 [PubMed: 26114620]

Gofshteyn JS et al. (2017) Cannabidiol as a Potential Treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the Acute and Chronic Phases J Child Neurol 32:35–40 doi:10.1177/0883073816669450 [PubMed: 27655472]

Gomes FV, Alves FH, Guimaraes FS, Correa FM, Resstel LB, Crestani CC (2013) Cannabidiol administration into the bed nucleus of the stria terminalis alters cardiovascular responses induced by acute restraint stress through 5-HT(1)A receptor Eur Neuropsychopharmacol 23:1096–1104 doi:10.1016/j.euroneuro.2012.09.007 [PubMed: 23041353]

Gomes FV, Reis DG, Alves FH, Correa FM, Guimaraes FS, Resstel LB (2012) Cannabidiol injected into the bed nucleus of the stria terminalis reduces the expression of contextual fear conditioning via 5-HT1A receptors Journal of psychopharmacology (Oxford, England) 26:104–113 doi:10.1177/0269881110389095

Gomes FV, Resstel LB, Guimaraes FS (2011) The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors Psychopharmacology (Berl) 213:465–473 doi:10.1007/s00213-010-2036-z [PubMed: 20945065]

Gray RA, Whalley BJ (2020) The proposed mechanisms of action of CBD in epilepsy Epileptic Disord 22:10–15 doi:10.1684/epd.2020.1135 [PubMed: 32053110]

Guy GW, Flint ME (2004) A Single Centre, Placebo-Controlled, Four Period, Crossover, Tolerability Study Assessing, Pharmacodynamic Effects, Pharmacokinetic Characteristics and Cognitive Profiles of a Single Dose of Three Formulations of Cannabis Based Medicine Extracts (CBMEs) (GWPD9901), Plus a Two Period Tolerability Study Comparing Pharmacodynamic Effects and Pharmacokinetic Characteristics of a Single Dose of a Cannabis Based Medicine Extract Given via Two Administration Routes (GWPD9901 EXT) Journal of Cannabis Therapeutics 3:35–77 doi:10.1300/J175v03n03_03

Hallak JE et al. (2010) Performance of schizophrenic patients in the Stroop Color Word Test and electrodermal responsiveness after acute administration of cannabidiol (CBD) Braz J Psychiatry 32:56–61 doi:10.1590/s1516-44462010000100011 [PubMed: 20339735]

Haney M et al. (2016) Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 41:1974–1982 doi:10.1038/npp.2015.367 [PubMed: 26708108]

Hartmann A, Lisboa SF, Sonego AB, Coutinho D, Gomes FV, Guimaraes FS (2019) Cannabidiol attenuates aggressive behavior induced by social isolation in mice: Involvement of 5-HT1A and CB1 receptors Prog Neuropsychopharmacol Biol Psychiatry 94:109637 doi:10.1016/j.pnpbp.2019.109637 [PubMed: 31054943]

Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC (1991) Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study J Neurosci 11:563–583 [PubMed: 1992016]

Hess EJ et al. (2016) Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex Epilepsia 57:1617–1624 doi:10.1111/epi.13499 [PubMed: 27696387]

Highlights of Prescribing Information. (2018). https://www.epidiolex.com/sites/default/files/pdfs/EPIDIOLEX_Full_Prescribing_Information_04_16_2020.pdf.

Hindocha C et al. (2018) Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal Addiction 113:1696–1705 doi:10.1111/add.14243

Hundal H et al. (2018) The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group Journal of psychopharmacology (Oxford, England) 32:276–282 doi:10.1177/0269881117737400

Hurd YL et al. (2019) Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial Am J Psychiatry 176:911–922 doi:10.1176/appi.ajp.2019.18101191 [PubMed: 31109198]

Iannotti FA et al. (2014) Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability ACS chemical neuroscience 5:1131–1141 doi:10.1021/cn5000524 [PubMed: 25029033]

Iannotti FA et al. (2019) Effects of non-euphoric plant cannabinoids on muscle quality and performance of dystrophic mdx mice Br J Pharmacol 176:1568–1584 doi:10.1111/bph.14460 [PubMed: 30074247]

Irving PM et al. (2018) A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis Inflamm Bowel Dis 24:714–724 doi:10.1093/ibd/izy002 [PubMed: 29538683]

Jadoon KA et al. (2016) Efficacy and Safety of Cannabidiol and Tetrahydrocannabivarin on Glycemic and Lipid Parameters in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Pilot Study Diabetes Care 39:1777–1786 doi:10.2337/dc16-0650 [PubMed: 27573936]

Jadoon KA, Tan GD, O'Sullivan SE (2017) A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study JCI Insight 2 doi:10.1172/jci.insight.93760

Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA (1974) Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man Eur J Pharmacol 28:172–177 doi:10.1016/0014-2999(74)90129-0 [PubMed: 4609777]

Kossakowski R, Schlicker E, Toczek M, Weresa J, Malinowska B (2019) Cannabidiol Affects the Bezold-Jarisch Reflex via TRPV1 and 5-HT3 Receptors and Has Peripheral Sympathomimetic Effects in Spontaneously Hypertensive and Normotensive Rats Frontiers in pharmacology 10:500 doi:10.3389/fphar.2019.00500 [PubMed: 31178718]

Laprairie RB, Bagher AM, Kelly MEM, Denovan-Wright EM (2015) Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor British Journal of Pharmacology 172:4790–4805 doi:10.1111/bph.13250 [PubMed: 26218440]

Lazarini-Lopes W, Do Val-da Silva RA, da Silva-Junior RMP, Leite JP, Garcia-Cairasco N (2020) The anticonvulsant effects of cannabidiol in experimental models of epileptic seizures: From behavior and mechanisms to clinical insights Neurosci Biobehav Rev 111:166–182 doi:10.1016/j.neubiorev.2020.01.014 [PubMed: 31954723]

Lee JLC, Bertoglio LJ, Guimarães FS, Stevenson CW (2017) Cannabidiol regulation of emotion and emotional memory processing: relevance for treating anxiety-related and substance abuse disorders British journal of pharmacology 174:3242–3256 doi:10.1111/bph.13724 [PubMed: 28268256]

Leweke FM et al. (2012) Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia Translational psychiatry 2:e94 doi:10.1038/tp.2012.15 [PubMed: 22832859]

Li H et al. (2020) Overview of cannabidiol (CBD) and its analogues: Structures, biological activities, and neuroprotective mechanisms in epilepsy and Alzheimer's disease Eur J Med Chem 192:112163 doi:10.1016/j.ejmech.2020.112163 [PubMed: 32109623]

Liebling JP, Clarkson NJ, Gibbs BW, Yates AS, O'Sullivan SE (2020) An Analysis of Over-the-Counter Cannabidiol Products in the United Kingdom Cannabis and Cannabinoid Research doi:10.1089/can.2019.0078

Ligresti A et al. (2006) Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma J Pharmacol Exp Ther 318:1375–1387 doi:10.1124/jpet.106.105247 [PubMed: 16728591]

Linares IM, Zuardi AW, Pereira LC, Queiroz RH, Mechoulam R, Guimarães FS, Crippa JA (2019) Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test Brazilian Journal of Psychiatry 41:9–14

Madden K, Tanco K, Bruera E (2020) Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol Pediatrics 145 doi:10.1542/peds.2019-3256

Manini AF et al. (2015) Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans J Addict Med 9:204–210 doi:10.1097/adm.0000000000000118 [PubMed: 25748562]

Martin-Santos R et al. (2012) Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers Current pharmaceutical design 18:4966–4979 doi:10.2174/138161212802884780 [PubMed: 22716148]

Massi P et al. (2008) 5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the antitumor activity of cannabidiol, a non-psychoactive cannabinoid J Neurochem 104:1091–1100 doi:10.1111/j.1471-4159.2007.05073.x [PubMed: 18028339]

McGuire P et al. (2018) Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial Am J Psychiatry 175:225–231 doi:10.1176/appi.ajp.2017.17030325 [PubMed: 29241357]

McPartland JM, Duncan M, Di Marzo V, Pertwee RG (2015) Are cannabidiol and Delta(9) - tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review Br J Pharmacol 172:737–753 doi:10.1111/bph.12944 [PubMed: 25257544]

Millar SA, Stone NL, Yates AS, O'Sullivan SE (2018) A Systematic Review on the Pharmacokinetics of Cannabidiol in Humans Frontiers in pharmacology 9:1365 [PubMed: 30534073]

Morelli MB et al. (2014) The effects of cannabidiol and its synergism with bortezomib in multiple myeloma cell lines. A role for transient receptor potential vanilloid type-2 Int J Cancer 134:2534–2546 doi:10.1002/ijc.28591 [PubMed: 24293211]

Morgan CJ, Das RK, Joye A, Curran HV, Kamboj SK (2013) Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings Addict Behav 38:2433–2436 doi:10.1016/j.addbeh.2013.03.011 [PubMed: 23685330]

Morgan CJA, Freeman TP, Hindocha C, Schafer G, Gardner C, Curran HV (2018) Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function Translational psychiatry 8:181 doi:10.1038/s41398-018-0191-x [PubMed: 30185793]

Nabissi M et al. (2015) Cannabidiol stimulates Aml-1a-dependent glial differentiation and inhibits glioma stem-like cells proliferation by inducing autophagy in a TRPV2-dependent manner Int J Cancer 137:1855–1869 doi:10.1002/ijc.29573 [PubMed: 25903924]

Nabissi M, Morelli MB, Santoni M, Santoni G (2013) Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents Carcinogenesis 34:48–57 doi:10.1093/carcin/bgs328 [PubMed: 23079154]

Naftali T et al. (2017) Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial Dig Dis Sci 62:1615–1620 doi:10.1007/s10620-017-4540-z [PubMed: 28349233]

Nichols JM, Kaplan BLF (2020) Immune Responses Regulated by Cannabidiol Cannabis and cannabinoid research 5:12–31 doi:10.1089/can.2018.0073 [PubMed: 32322673]

Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C (2004) Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies Anaesthesia 59:440–452 doi:10.1111/j.1365-2044.2004.03674.x [PubMed: 15096238]

Nunez E et al. (2004) Cannabinoid CB2 receptors are expressed by perivascular microglial cells in the human brain: an immunohistochemical study Synapse 53:208–213 doi:10.1002/syn.20050 [PubMed: 15266552]

Ohlsson A, Lindgren JE, Andersson S, Agurell S, Gillespie H, Hollister LE (1986) Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration Biomed Environ Mass Spectrom 13:77–83 doi:10.1002/bms.1200130206 [PubMed: 2937482]

Petrosino S, Verde R, Vaia M, Allara M, Iuvone T, Di Marzo V (2018) Anti-inflammatory Properties of Cannabidiol, a Nonpsychotropic Cannabinoid, in Experimental Allergic Contact Dermatitis J Pharmacol Exp Ther 365:652–663 doi:10.1124/jpet.117.244368 [PubMed: 29632236]

Pisanti S et al. (2017) Cannabidiol: State of the art and new challenges for therapeutic applications Pharmacol Ther 175:133–150 doi:10.1016/j.pharmthera.2017.02.041 [PubMed: 28232276]

Poklis JL, Mulder HA, Peace MR (2019) The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids Forensic Science International 294:e25–e27 doi:10.1016/j.forsciint.2018.10.019 [PubMed: 30442388]

Qin N, Neeper MP, Liu Y, Hutchinson TL, Lubin ML, Flores CM (2008) TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons J Neurosci 28:6231–6238 doi:10.1523/jneurosci.0504-08.2008 [PubMed: 18550765]

Resstel LB, Tavares RF, Lisboa SF, Joca SR, Correa FM, Guimaraes FS (2009) 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats Br J Pharmacol 156:181–188 doi:10.1111/j.1476-5381.2008.00046.x [PubMed: 19133999]

Russo EB, Burnett A, Hall B, Parker KK (2005) Agonistic properties of cannabidiol at 5-HT1a receptors Neurochem Res 30:1037–1043 doi:10.1007/s11064-005-6978-1 [PubMed: 16258853]

Sartim AG, Guimaraes FS, Joca SR (2016) Antidepressant-like effect of cannabidiol injection into the ventral medial prefrontal cortex-Possible involvement of 5-HT1A and CB1 receptors Behav Brain Res 303:218–227 doi:10.1016/j.bbr.2016.01.033 [PubMed: 26801828]

Schier AR, Ribeiro NP, Silva AC, Hallak JE, Crippa JA, Nardi AE, Zuardi AW (2012) Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug Braz J Psychiatry 34 Suppl 1:S104–110 doi:10.1590/s1516-44462012000500008

Schoedel KA et al. (2018) Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial Epilepsy Behav 88:162–171 doi:10.1016/j.yebeh.2018.07.027 [PubMed: 30286443]

Soares VP, Campos AC (2017) Evidences for the Anti-panic Actions of Cannabidiol Curr Neuropharmacol 15:291–299 doi:10.2174/1570159x14666160509123955 [PubMed: 27157263]

Soares VP, Campos AC, Bortoli VC, Zangrossi H, Jr., Guimaraes FS, Zuardi AW (2010) Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors Behav Brain Res 213:225–229 doi:10.1016/j.bbr.2010.05.004 [PubMed: 20457188]

Solowij N et al. (2019) A randomised controlled trial of vaporised Delta(9)-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects Eur Arch Psychiatry Clin Neurosci 269:17–35 doi:10.1007/s00406-019-00978-2 [PubMed: 30661105]

Sonego AB, Gomes FV, Del Bel EA, Guimaraes FS (2016) Cannabidiol attenuates haloperidol-induced catalepsy and c-Fos protein expression in the dorsolateral striatum via 5-HT1A receptors in mice Behav Brain Res 309:22–28 doi:10.1016/j.bbr.2016.04.042 [PubMed: 27131780]

Spindle TR et al. (2020a) Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users Drug Alcohol Depend:107937 doi:10.1016/j.drugalcdep.2020.107937 [PubMed: 32247649]

Spindle TR, Cone EJ, Kuntz D, Mitchell JM, Bigelow GE, Flegel R, Vandrey R (2020b) Urinary Pharmacokinetic Profile of Cannabinoids Following Administration of Vaporized and Oral Cannabidiol and Vaporized CBD-Dominant Cannabis Journal of analytical toxicology 44:109–125 doi:10.1093/jat/bkz080 [PubMed: 31682266]

Stout SM, Cimino NM (2014) Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review Drug Metabolism Reviews 46:86–95 doi:10.3109/03602532.2013.849268 [PubMed: 24160757]

Sultan SR, O'Sullivan SE, England TJ (2020) The effects of acute and sustained cannabidiol dosing for seven days on the haemodynamics in healthy men: A randomised controlled trial British journal of clinical pharmacology doi:10.1111/bcp.14225

Szaflarski JP et al. (2018) Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study Epilepsy Behav 87:131–136 doi:10.1016/j.yebeh.2018.07.020 [PubMed: 30100226]

Taylor L, Crockett J, Tayo B, Morrison G (2019) A Phase 1, Open-Label, Parallel-Group, Single-Dose Trial of the Pharmacokinetics and Safety of Cannabidiol (CBD) in Subjects With Mild to Severe Hepatic Impairment J Clin Pharmacol 59:1110–1119 doi:10.1002/jcph.1412 [PubMed: 30921490]

Taylor L, Gidal B, Blakey G, Tayo B, Morrison G (2018) A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects CNS Drugs 32:1053–1067 doi:10.1007/s40263-018-0578-5 [PubMed: 30374683]

Tham M, Yilmaz O, Alaverdashvili M, Kelly MEM, Denovan-Wright EM, Laprairie RB (2019) Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors Br J Pharmacol 176:1455–1469 doi:10.1111/bph.14440 [PubMed: 29981240]

Thiele EA et al. (2018) Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial Lancet 391:1085–1096 doi:10.1016/s0140-6736(18)30136-3 [PubMed: 29395273]

Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ (2006) Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study J Glaucoma 15:349–353 doi:10.1097/01.ijg.0000212260.04488.60 [PubMed: 16988594]

Turna J, Syan SK, Frey BN, Rush B, Costello MJ, Weiss M, MacKillop J (2019) Cannabidiol as a Novel Candidate Alcohol Use Disorder Pharmacotherapy: A Systematic Review Alcohol Clin Exp Res 43:550–563 doi:10.1111/acer.13964 [PubMed: 30698831]

van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M (2019) An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia Pain 160:860–869 doi:10.1097/j.pain.0000000000001464 [PubMed: 30585986]

Van Sickle MD et al. (2005) Identification and functional characterization of brainstem cannabinoid CB2 receptors Science 310:329–332 doi:10.1126/science.1115740 [PubMed: 16224028]

Vilela LR et al. (2017) Anticonvulsant effect of cannabidiol in the pentylenetetrazole model: Pharmacological mechanisms, electroencephalographic profile, and brain cytokine levels Epilepsy Behav 75:29–35 doi:10.1016/j.yebeh.2017.07.014 [PubMed: 28821005]

Wade DT, Robson P, House H, Makela P, Aram J (2003) A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms Clinical Rehabilitation 17:21–29 doi:10.1191/0269215503cr581oa [PubMed: 12617376]

Wheless JW et al. (2019) Pharmacokinetics and Tolerability of Multiple Doses of Pharmaceutical-Grade Synthetic Cannabidiol in Pediatric Patients with Treatment-Resistant Epilepsy CNS Drugs 33:593–604 doi:10.1007/s40263-019-00624-4 [PubMed: 31049885]

Wiemer-Kruel A, Stiller B, Bast T (2019) Cannabidiol Interacts Significantly with Everolimus-Report of a Patient with Tuberous Sclerosis Complex Neuropediatrics 50:400–403 doi:10.1055/s-0039-1695786 [PubMed: 31539915]

Xu DH, Cullen BD, Tang M, Fang Y (2020) The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities Curr Pharm Biotechnol 21:390–402 doi:10.2174/1389201020666191202111534 [PubMed: 31793418]

Yang KH, Galadari S, Isaev D, Petroianu G, Shippenberg TS, Oz M (2010) The nonpsychoactive cannabinoid cannabidiol inhibits 5-hydroxytryptamine3A receptor-mediated currents in Xenopus laevis oocytes J Pharmacol Exp Ther 333:547–554 doi:10.1124/jpet.109.162594 [PubMed: 20160007]

Yeshurun M et al. (2015) Cannabidiol for the Prevention of Graft-versus-Host-Disease after Allogeneic Hematopoietic Cell Transplantation: Results of a Phase II Study Biol Blood Marrow Transplant 21:1770–1775 doi:10.1016/j.bbmt.2015.05.018 [PubMed: 26033282]

Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SR (2010) Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors Br J Pharmacol 159:122–128 doi:10.1111/j.1476-5381.2009.00521.x [PubMed: 20002102]

Zanger UM, Schwab M (2013) Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation Pharmacol Ther 138:103–141 doi:10.1016/j.pharmthera.2012.12.007 [PubMed: 23333322]

Zuardi AW, Cosme RA, Graeff FG, Guimarães FS (1993) Effects of ipsapirone and cannabidiol on human experimental anxiety Journal of Psychopharmacology 7:82–88 doi:10.1177/026988119300700112 [PubMed: 22290374]

Zuardi AW et al. (2009) Cannabidiol for the treatment of psychosis in Parkinson's disease Journal of psychopharmacology (Oxford, England) 23:979–983 doi:10.1177/0269881108096519

Zuardi AW, Rodrigues NP, Silva AL, Bernardo SA, Hallak JEC, Guimarães FS, Crippa JAS (2017) Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of Cannabidiol during Public Speaking in Real Life Frontiers in pharmacology 8 doi:10.3389/fphar.2017.00259

**Table 1.**

Pharmacokinetic studies of cannabidiol (CBD) in humans.

| Reference | Population | Route | Dose | Matrix | Analytical Method | $T_{max}$ | $C_{max}$ | $t_{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| Birnbaum et al. (2019) | Adults w/ refractory epilepsy n=8 | Oral (Viero Health Violet Formulation) | 200–300 mg | Plasma | Negative-ion mode electro-spray-ionization liquid chromatography-tandem mass spectrometry | Fed: Mean: 2.4 h Range: 1–6 h Fasting: Mean: 3.2 h Range: 2–5 h | Fed: 0.45 (ng/ml)/mg Fasting: 0.03 (ng/ml)/mg | Fed: 24.3 h Fasting: 38.9 h |
| Consroe et al. (1991a) | Huntington's patients n=14 | Oral (National Institute on Drug Abuse) | 10 mg/kg daily for 6 weeks | Plasma | Capillary gas chromatography/ion trap mass spectroscopy | -- | -- | Mean: 68.2 h Range: 41.4–113 h |
| Devinsky et al. (2018b) | 4–10 year old children w/ Dravet syndrome n=34 | Oral solution (Epidiolex®) | 1.5 mg/kg once<br>5 mg/kg daily<br>10 mg/kg daily<br>20 mg/kg daily | Plasma | Ultra-performance liquid chromatography with tandem mass spectrometry | 2.5 h<br>Day 22: 2.5 h<br>Day 22: 5 h<br>Day 22: 2.5 h | 29.3–37.6 ng/ml<br>Day 22: 130 ng/ml<br>Day 22: 288 ng/ml<br>Day 22: 380 ng/ml | -- |
| Guy and Flint (2004) | Healthy adults w/ a history of cannabis use n=12 | Sublingual (GW-3009–01) | 20 mg | Plasma | -- | 2.17 h | 2.05 ng/ml | -- |
| Haney et al. (2016) | Adult regular cannabis users n=8 | Oral (STI Pharmaceuticals) | 800 mg | Plasma | Liquid/liquid extraction, derivatization, and gas chromatography-tandem mass spectrometry | Mean: 3 h Range: 2–6 h | Mean: 77.9 ng/ml Range: 1.6–271.9 ng/ml | -- |
| Ohlsson et al. (1986) | Adult men w/ a history of cannabis use n=5 | Intravenous<br>Smoking | 20 mg<br>19 mg | Plasma | Gas chromatography mass spectrometry | -- | Mean: 686 SD: 239<br>Mean: 110 SD: 55 | Mean: 24 h<br>Mean: 31 h |
| Schoedel et al. (2018) | Adult polydrug users n=41 | Oral solution (Epidiolex®) | 750 mg 1500 mg 4500 mg | Plasma | -- | 5.11 h<br>6.13 h<br>4.07 h | 336.2 ng/ml<br>524.5 ng/ml<br>426.9 ng/ml | -- |
| Taylor et al. (2018) | Healthy adults n=6/dose | Oral solution (Epidiolex®) | 1500 mg<br>3000 mg<br>4500 mg<br>6000 mg | Plasma | High-performance liquid chromatography with tandem mass spectrometry | Median: 4 h Range: 3–5 h<br>Median: 5 h Range: 3–5 h<br>Median: 5 h Range: 5–5 h<br>Median: 5 h Range: 3–5 h | Mean: 292.4 ng/ml<br>Mean: 533.0 ng/ml<br>Mean: 722.1 ng/ml<br>Mean: 782.0 ng/ml | Mean: 14.43 h<br>Mean: 14.39 h<br>Mean: 16.61 h<br>Mean: 15.42 h |

| Reference | Population | Route | Dose | Matrix | Analytical Method | $T_{max}$ | $C_{max}$ | $t_{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| | n=9/dose | | 750 mg twice daily for 6 days | | | Day 1 AM<br>Median: 5 h<br>Range: 2.5–5 h | Day 1 AM<br>Mean: 290.8 ng/ml | |
| | | | | | | Day 7 AM<br>Median: 3 h<br>Range: 2.5–5 h | Day 7 AM<br>Mean: 330.3 ng/ml | Day 7 AM<br>Mean: 56.41 h |
| | n=12/dose | | 1500 mg twice daily for 6 days | | | Day 1 AM<br>Median: 5 h<br>Range: 2.5–5 h | Day 1 AM<br>Mean: 361.8 ng/ml | |
| | | | | | | Day 7 AM<br>Median: 3 h<br>Range: 2–4 h | Day 7 AM<br>Mean: 541.2 ng/ml | Day 7 AM<br>Mean: 60.54 h |
| | | | 1500 mg | | | Fed:<br>Mean: 3 h<br>Range: 1.5–5 h | Fed: 1628 ng/ml | Fed: 24.4 h |
| | | | | | | Fasting:<br>Mean: 3.5 h<br>Range: 2.5–5.03 h | Fasting: 335.4 ng/ml | Fasting: 30.33 h |
| Taylor et al. (2019) | Adults w/ mild to severe hepatic impairment vs. healthy controls | Oral solution (Epidiolex®) | 200 mg | Plasma | Liquid chromatography with tandem mass spectrometry | | | |
| | Healthy adults n=8 | | | | | Mean: 2.3 h | Mean: 148 ng/ml | Mean: 8.58 h |
| | Mild hepatic impairment n=8 | | | | | Mean: 2.8 h | Mean: 233 ng/ml | Mean: 15.7 h |
| | Moderate hepatic impairment n=8 | | | | | Mean: 2.0 h | Mean: 354 ng/ml | Mean: 20.5 h |
| | Severe hepatic impairment n=6 | | | | | Mean: 2.5 h | Mean: 381 ng/ml | Mean: 22.1 h |
| Wheless et al. (2019) | Children w/ treatment-resistant epilepsy n=20 | Oral solution (INSYS Manufacturing LLC) | 5 mg/kg | Plasma | High-performance liquid chromatography with tandem mass spectrometry | Median: 2.6 h<br>Range: 1–8 h | Mean: 59.03 ng/ml | Mean: 31.3 h |
| | n=20 | | 10 mg/kg | | | Median 4.0 h<br>Range: 1–8.1 h | Mean: 110.5 ng/ml | Mean: 33.5 h |
| | n=21 | | 20 mg/kg | | | Median 3.2 h<br>Range: 1–24 h | Mean: 256.9 ng/ml | Mean: 21.6 h |
| | n=20 | | 10 mg/kg daily for 6 days | | | Day 6:<br>Median: 3 h<br>Range: 1–4.2 h | Day 6:<br>Mean: 119.6 ng/ml | |
| | n=20 | | 20 mg/kg daily for 6 days | | | Day 6:<br>Median: 2 h<br>Range: 0–6 h | Day 6:<br>Mean: 220 ng/ml | |

| Reference | Population | Route | Dose | Matrix | Analytical Method | $T_{max}$ | $C_{max}$ | $t_{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| | n=21 | | 40 mg/kg daily for 6 days | | | Day 6: Median: 3 h Range: 0–6 h | Day 6: Mean: 426.8 ng/ml | |

**Table 2.**

Pharmacokinetic studies of cannabidiol (CBD) metabolites 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD in humans.

| Reference | Route & Population | CBD Dose | 6-OH-CBD | | | 7-OH-CBD | | | 7-COOH-CBD | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $T_{max}$ (h) | $C_{max}$ (geometric mean, ng/ml) | $t_{1/2}$ (mean h) | $T_{max}$ (h) | $C_{max}$ (geometric mean, ng/ml) | $t_{1/2}$ (mean h) | $T_{max}$ (h) | $C_{max}$ (geometric mean, ng/ml) | $t_{1/2}$ (mean h) |
| Taylor et al. (2018) | Epidiolex® in healthy adults | 1500 mg | Median: 4 Range: 2.5–4 | 10.7 | 40.75 | Median: 3.5 Range: 2.5–4 | 238.7 | 18.70 | Median: 4 Range: 4–5 | 3060 | 25.98 |
| | | 3000 mg | Median: 4.5 Range: 2.5–5 | 14.4 | 22.78 | Median: 4.5 Range: 3–5 | 332.2 | 15.42 | Median: 5 Range: 4–5 | 3557 | 23.88 |
| | | 4500 mg | Median: 5 Range: 4–5 | 14.5 | 33.92 | Median: 5 Range: 4–5 | 404.8 | 14.89 | Median: 5 Range: 4–8 | 5120 | 25.18 |
| | | 6000 mg | Median: 5 Range: 3–5 | 23.5 | 28.67 | Median: 5 Range: 3–5 | 515.8 | 14.46 | Median: 5 Range: 4–8 | 4591 | 30.24 |
| | | 750 mg twice daily for 6 days | Day 1 AM Median: 5 Range: 2.5–6 | Day 1 AM 8.2 | Day 1 AM -- | Day 1 AM Median: 4 Range: 25–6 | Day 1 AM 123.0 | Day 1 AM -- | Day 1 AM Median: 5 Range: 4–5 | Day 1 AM 2785 | Day 1 AM -- |
| | | | Day 7 AM Median: 2.5 Range: 2–5 | Day 7 AM 12.8 | Day 7 AM 21.54 | Day 7 AM Median: 2.5 Range: 2–5 | Day 7 AM 152.6 | Day 7 AM 24.73 | Day 7 AM Median: 4 Range: 3–5 | Day 7 AM 9824 | Day 7 AM 21.32 |
| | | 1500 mg twice daily for 6 days | Day 1 AM Median: 4 Range: 3–5 | Day 1 AM 9.0 | Day 1 AM -- | Day 1 AM Median: 4 Range: 3–5 | Day 1 AM 139.5 | Day 1 AM -- | Day 1 AM Median: 5 Range: 4–12 | Day 1 AM 2748 | Day 1 AM -- |
| | | | Day 7 AM Median: 3 Range: 2.5–5 | Day 7 AM 16.3 | Day 7 AM 82.21 | Day 7 AM Median: 3 Range: 2.5–5 | Day 7 AM 187.9 | Day 7 AM 31.70 | Day 7 AM Median: 3 Range: 0.5–5 | Day 7 AM 16,306 | Day 7 AM 22.00 |
| Taylor et al. (2019) | Epidiolex® in adults w/ mild to severe hepatic impairment vs. healthy controls | 200 mg | | | | | | | | | |
| | Healthy adults | | Mean: 2.5 | 3.19 | 13.2 | Mean: 2.8 | 41.8 | 13.3 | Mean: 4.5 | 823 | 19.8 |
| | Mild hepatic impairment | | Mean: 2.5 | 5.78 | 17.5 | Mean: 3.5 | 54.9 | 14.8 | Mean: 3.5 | 706 | 21.8 |
| | Moderate hepatic impairment | | Mean: 1.5 | 7.56 | 20.8 | Mean: 2.0 | 76.4 | 15.6 | Mean: 2.8 | 804 | 22.8 |

*Psychopharmacology (Berl)*. Author manuscript; available in PMC 2022 January 01.

| Reference | Route & Population | CBD Dose | 6-OH-CBD | | | 7-OH-CBD | | | 7-COOH-CBD | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $T_{max}$ (h) | $C_{max}$ (geometric mean, ng/ml) | $t_{1/2}$ (mean h) | $T_{max}$ (h) | $C_{max}$ (geometric mean, ng/ml) | $t_{1/2}$ (mean h) | $T_{max}$ (h) | $C_{max}$ (geometric mean, ng/ml) | $t_{1/2}$ (mean h) |
| | Severe hepatic impairment | | Mean: 2.0 | 5.35 | 20.3 | Mean: 3.5 | 45.5 | 21.7 | Mean: 4.0 | 221 | Not calculatable |
| Wheless et al. (2019) | Oral CBD solution in children w/ treatment-resistant epilepsy | 5 mg/kg | -- | -- | -- | Median 2.6<br>Range: 1–6.1 | 22.03 | 18.4 | -- | -- | -- |
| | | 10 mg/kg | | | | Median 4.0<br>Range: 1–12 | 34.56 | 25.6 | | | |
| | | 20 mg/kg | | | | Median: 3.1<br>Range: 1–121 | 71.7 | 14.2 | | | |
| | | 10 mg/kg daily for 6 days | | | | Day 6:<br>Median: 2.1<br>Range: 1–4.1 | Day 6:<br>65.6 | -- | | | |
| | | 20 mg/kg daily for 6 days | | | | Day 6:<br>Median: 2<br>Range: 1–6 | Day 6:<br>97.1 | -- | | | |
| | | 40 mg/kg daily for 6 days | | | | Day 6:<br>Median: 2<br>Range: 0–5.9 | Day 6: 217.7 | -- | | | |

**Table 3.**

Clinical studies of CBD effects on neurological disorders.

| Reference | Study Sample | CBD Dose and Route | CBD Formulation | Study Details | Summary Outcomes |
|---|---|---|---|---|---|
| Chagas et al. (2014) | Parkinson's disease (n=21) | 75 or 300 mg/day, p.o. for 6 weeks | Gelatin capsule containing 99.9% pure CBD (THC-Pharma) dissolved in corn oil | Randomized, double-blind, placebo-controlled | 300 (but not 75) mg CBD was associated with better scores on the Parkinson's Disease Questionnaire. Similar scores were found on the Unified Parkinson's Disease rating scale with CBD and placebo treatment |
| Consroe et al. (1991b) | Huntington's disease (n=15) | 10 mg/kg/day, p.o., for 5 weeks | Gelatin capsule containing CBD (National Institute on Drug Abuse) dissolved in sesame oil | Randomized, double-blind, placebo-controlled, crossover | No improvement of Huntington's disease-related symptoms |
| Cunha et al. (1980) | Generalized epilepsy (n=15) | 200–300 mg, p.o./daily for up to 18 weeks | Gelatin capsule containing CBD or glucose (placebo) | Randomized, double-blind, placebo-controlled | Reduced reported monthly seizure episodes on scale of 0–3 |
| Devinsky et al. (2016) | Patients ages 1–30 with severe, intractable, treatment-resistant childhood onset seizures (n=137) | Up to 50 mg/kg/day, p.o. | Epidiolex® | Open-label | 36.5% decrease in median monthly seizures |
| Devinsky et al. (2017) | Dravet Syndrome patients ages 2–18 (n=120) | Escalated to 20 mg/kg/day, p.o., over two weeks, followed by 20 mg/kg/day for 12 weeks | Epidiolex® | Randomized, double-blind, placebo-controlled | CBD decreased median monthly motor seizers by 38.9% (placebo decrease was 13.3%) |
| Devinsky et al. (2018a) | Lennox-Gastaut patients, ages 2–55 (n=212) | 10 or 20 mg/kg/day, p.o. for 14 weeks | Epidiolex® | Randomized, double-blind, placebo-controlled | 10 or 20 mg/kg/day oral CBD had a 37.2% and 41.9% decrease in drop-seizure activity from baseline, respectively, compared to a 17.2% decrease in patients who received placebo |
| Gofshteyn et al. (2017) | Febrile infection-related epilepsy (n=7) | Titrated to 15–25 mg/kg/day | Epidiolex® | Open-label case series (emergency/expanded access) | 6 out of 7 patients had decreases in seizure frequency |
| (Hess et al. 2016) | Tuberous Sclerosis Complex (n=18) | Titrated to 50 mg/kg/day | Epidiolex® | Open-label, expanded access | Decreased median monthly seizure frequency from 22 at baseline to 13.3 after 3 months of treatment (48.8% decrease). |
| Szaflarski et al. (2018) | Adults and children with various types of epilepsy (n=139) | Titrated up to 50 mg/kg/day, p.o., for 12–48 weeks | Epidiolex® | Open-label, add-on | Decreased mean Chalfont Seizure Severity Scores from 80.7 to 39.3 after 12 weeks of treatment. Scores were stable from week 12 to week 48. |
| Thiele et al. (2018) | Lennox-Gastaut patients ages 2–55 (n=171) | 20 mg/kg/day, p.o., for 14 weeks | Epidiolex® | Randomized, double-blind, placebo-controlled | CBD decreased drop seizures by 43.9%, placebo decreased drop-seizures by 21.8% |
| Zuardi et al. (2009) | Parkinson's disease (n=6) | 150 mg/day, p.o. Dose increased by 150 mg/day weekly for 4 weeks. | Gelatin capsule containing 99.9% pure CBD (THC-Pharma) dissolved in corn oil | Open-label, pilot | CBD was associated with improved scores on the Brief Psychiatric Rating Scale and the Parkinson's Psychosis Questionnaire |

**Table 4.**

Clinical studies of CBD effects on pain, inflammation, and immune function.

| Reference | Study Sample | CBD Dose and Route | CBD Formulation | Study Details | Summary Outcomes |
|---|---|---|---|---|---|
| Capano et al. (2020) | Patients on opioids for chronic pain (n=94) | Self-titrated to 30 mg/day, p.o. | CBD-rich hemp extract | Exploratory | 50 out of 94 patients reduced their opioid intake |
| Couch et al. (2019) | Male participants who received aspirin to increase absorption of lactulose and mannitol (n=38) | 600 mg, p.o. | 99.65% pure CBD in cellulose (Artelo Biosciences) | Randomized, double-blind, placebo-controlled | Mannitol and lactulose absorption were decreased after treatment with CBD |
| Irving et al. (2018) | Ulcerative colitis (n=6) | Titrated up to 250 mg/day, p.o. for 10 weeks | CBD-rich botanical extract in a gelatin capsule | Randomized, doublebind, placebo-controlled | CBD did not improve remission rates |
| Jadoon et al. (2016) | Type II diabetes (n=62) | 200 mg/day (route unknown) for 13 weeks | | Randomized, double-blind, placebo-controlled | CBD did not improve glycemic control |
| Naftali et al. (2017) | Crohn's disease (n=19) | 20 mg/day, sublingual, for 8 weeks | 99.5% pure CBD extracted in house and dissolved in olive oil | Randomized, double-blind, placebo-controlled | No change in Crohn's disease activity index |
| Notcutt et al. (2004) | Chronic pain (primarily due to multiple sclerosis) (n=34) | 2.5 mg, sublingual spray for 8 weeks | Botanical CBD extract dissolved in tetrafluoroethane 80%, ethanol 20% for n=6 and in ethanol 50%, propylene glycol 50% for n=28 | Randomized, double-blind, placebo-controlled, crossover | No improvement of chronic pain on a visual analog scale |
| Tomida et al. (2006) | Ocular hypertension or glaucoma (n=6) | 20 or 40 mg, sublingual spray | provided by GW Pharmaceuticals | Randomized, double-blind, placebo-controlled, crossover | 20 mg CBD did not alter intraocular pressure, 40 mg CBD increased intraocular pressure |
| van de Donk et al. (2019) | Chronic pain due to fibromyalgia (n=20) | 18.4 mg, vaporized (inhaled) | Bedrolite (18.4 mg CBD & < 1 mg THC), | Randomized, double-blind, placebo-controlled, crossover | No improvement of experimental pressure or electrical pain |
| Wade et al. (2003) | Pain due to multiple sclerosis, spinal injury, brachial plexus lesions, or amputation (n=20) | 2.5–120 mg/day, sublingual spray | CBD extract in unknown solvent (GW Pharmaceuticals) | Randomized, double-blind, placebo-clntrllled, crossover | CBD treatment was associated with decrease pain on a visual analog scale. CBD did not improve spasms, coordination, bladder control, or emotional well-being. |
| Xu et al. (2020) | Neuropathic pain in the lower extremities due to various etiologies (n=29) | 250 mg/3 fl. oz. topical CBD applied up to 4 times a day for 4–8 weeks | Theramu Relieve CBD compound Cream (Theramu) or emu oil (placebo) | Randomized, double-blind, placebo controlled | CBD decreased ratings of "intense, sharp, cold, and itchy" on the Neuropathic Pain Scale |
| Yeshurun et al. (2015) | Patients undergoing hematopoietic cell transplantation (n=48) | 300 mg/day, p.o. prophylactic starting 7 days before transplantation and continuing until day 30 | CBD (STI pharmaceuticals) dissolved in olive oil at 2.5% concentration | Historical control | Patients that received prophylactic CBD had lower rates of graft-versus-host-disease compared to a historical control of 101 patients |

**Table 5.**

Clinical studies of CBD effects on psychiatric disorders and substance use.

| Reference | Study Sample | CBD Dose, and Route | Drug Formulation | Study Details | Summary Outcomes |
|---|---|---|---|---|---|
| Arkell et al. (2019) | Healthy adults (n=14) | 125 mg plant material, inhaled (vaporized) | 11% THC and <1% CBD<br>11% THC and 11% CBD<br><1% THC and <1% CBD<br>(placebo) (from Tilray) | Randomized, double-blind, placebo-controlled crossover | No subjective difference between THC and the THC +CBD combination |
| Appiah-Kusi et al. (2020) | Adults with high risk for psychosis (n=58) | 600 mg/day, p.o. for 1 weeks | Capsule (STI Pharmaceuticals) | Randomized, double-blind, placebo-controlled | No difference between patients that received CBD versus placebo on the Tier Social Stress Test |
| Bergamaschi et al. (2011) | Undergraduate students with social phobia (n=36) and healthy controls | 600 mg, p.o. | Gelatin capsule containing 99.9% pure CBD (SIT Pharmaceuticals and THC-Pharm) dissolved in corn oil | Randomized, double-blind, placebo-controlled | CBD decreased anxiety during a simulated public speaking test |
| Bhattacharyya et al. (2010) | Adults who experienced THC-induced psychosis (n=3) | 5 mg, I.V. | -- | Pseudorandomized, double-blind, crossover | CBD prevented the acute psychotic symptoms to THC (1.25 mg, I.V.) |
| Boggs et al. (2018) | Schizophrenia (n=36) | 600 mg/day, p.o. for 6 weeks | STI Pharmaceuticals | Randomized, double-blind, placebo-controlled | CBD did not affect scores on the MATRICS Consensus Cognitive Battery or the Positive and Negative Symptoms Scale |
| Borgwardt et al. (2008) | Healthy adults (n=15) | 600 mg, p.o. | Capsule | Pseudorandomized, double-blind, placebo-controlled, crossover | No effect of CBD on the Visual Analog Mood Scale, Spielberger State Trait Anxiety Inventory test, or Positive and Negative Symptoms Scale |
| Consroe et al. (1979) | Healthy adults (n=10) | 200 mg, p.o. | Gelatin capsule containing crystalline CBD (from Dr. R. Mechoulam) | Randomized, double-blind, placebo-controlled, crossover | Consumption of 1 g/kg alcohol with CBD resulted in lower blood alcohol concentration than only alcohol, but CBD did not alter the behavioral effects of alcohol |
| Crippa et al. (2011) | Men with generalized anxiety (n=10) | 400 mg, p.o. | Gelatin capsule containing 99.9% pure CBD (THC-Pharma) dissolved in corn oil | Randomized, double-blind, placebo-controlled, crossover | CBD reduced anxiety on a visual analog mood scale |
| Englund et al. (2013) | Healthy adults (n=22) | 600 mg, p.o. | Capsule (STI Pharmaceuticals) | Randomized, double-blind, placebo-controlled | CBD prevented THC (1.5 mg, I.V.) - induced paranoia via assessment with the State Social Paranoia Scale |
| Fusar-Poli et al. (2009) | Healthy adults (n=15) | 600 mg, p.o. | Gelatin capsule containing 99.9% pure CBD (THC-Pharma) | Randomized, double-blind, placebo-controlled, crossover | No effect of CBD on the Visual Analog Mood Scale, Spielberger State Trait Anxiety Inventory test, or Positive and Negative Symptoms Scale |
| Hallak et al. (2010) | Schizophrenia (n=28) | 300 or 600 mg, p.o. | Gelatin capsule containing CBD (from Dr. R. Mechoulam) | Double-blind, placebo-controlled | CBD had no effect on the Positive and Negative Symptom Scale, Brief Psychiatric Rating Scale, or performance on the Stroop Color Word Test |
| Haney et al. (2016) | Cannabis smokers (n=31) | 200, 400, or 800 mg, p.o. | Size 00 opaque capsule containing CBD (STI Pharmaceuticals) | Randomized, double-blind, placebo-controlled, crossover | CBD did not change the subjective intoxicating effects of smoked cannabis containing THC (5.08–5.30%), nor did it alter cannabis self-administration |

| Reference | Study Sample | CBD Dose, and Route | Drug Formulation | Study Details | Summary Outcomes |
|---|---|---|---|---|---|
| Hindocha et al. (2018) | Non-treatment seeking tobacco smokers undergoing abstinence (n=33) | 800 mg, p.o. | Opaque capsule containing pure synthetic CBD (STI Pharmaceuticals) | Randomized, double-blind, placebo-controlled, crossover | CBD decreased attention bias toward cigarette cues, but did not alter craving or withdrawal ratings |
| Hundal et al. (2018) | Adults with high trait paranoia and persecutory ideation (n=32) | 600 mg, p.o. | Gelatin capsule containing CBD (GW Pharmaceuticals) in Killophor EL and M1944CS | Randomized, double-blind, placebo-controlled | No significant difference between CBD and placebo on the State Social Paranoia Scale or the Community Assessment of Psychic Experiences questionnaire |
| Hurd et al. (2019) | Participants with heroin use disorder who were abstinent (n=42) | 400 or 800 mg., p.o. acute, or daily for three days | Epidiolex® | Randomized, double-blind, placebo-controlled | Acutely, CBD decreased drug-cue induced craving on a visual analog scale, but not heroin. One week after their last treatment, participants that received CBD still had lower scores on a visual analog scale for drug-cue induced craving.<br>Heroin craving (assessed by out of clinic questionnaire) was not altered by CBD.<br>Those who received CBD had lower scores on a visual analog scale of anxiety. |
| Karniol et al. (1974) | Healthy adults (n=40) | 15, 30, or 60 mg, p.o. | CBD (Makor Chemicals Ltd.) dissolved in 0.9 ml of ethanol and placed in 200 ml of orange juice | Double-blind, placebo-controlled | CBD inhibited the subjective effects of THC (30 mg, p.o.) on a scale of 0–4 |
| Leweke et al. (2012) | Schizophrenia (n=33) | Increasing to 800 mg/day over the first week, then 800 mg/day for 3 additional weeks | -- | Randomized, double-blind | CBD improved clinical symptoms compared to baseline. |
| Linares et al. (2019) | Healthy adult men (n=57) | 150, 300, or 600 mg, p.o. | Gelatin capsule containing 99.9% pure CBD (STI Pharmaceuticals) dissolved in corn oil | Randomized, double-blind, placebo-controlled | 300 mg (but not 150 or 600 mg) reduced anxiety during a simulated public speaking test. |
| Manini et al. (2015) | Healthy adults with experience with opioids (non-dependent) (n=17) | 400 or 800 mg, p.o. | Gelatin capsule containing 99.9% pure CBD (GW Pharmaceuticals) dissolved in corn oil | Double-blind, placebo-controlled, crossover | CBD did not alter the pharmacokinetics or adverse effects of 0.5 or 1.0 μg/kg I.V. fentanyl |
| Martin-Santos et al. (2012) | Healthy adult men (n=16) | 600 mg, p.o. | Opaque capsule with 99.9% pure CBD (THC-Pharm and STI Pharmaceuticals) | Randomized, double-blind, placebo-controlled, crossover | CBD did not alter scores on the Positive and Negative Symptoms Scale or on the Spielberger State Trait Anxiety Inventory |
| McGuire et al. (2018) | Schizophrenia (n=88) | 1000 mg/day for 6 weeks | Oral solution (GW Pharmaceuticals) | Randomized, double-blind, placebo-controlled | CBD decreased positive psychotic symptoms on the Positive and Negative Symptoms Scale and those who received CBD were rated as better on the Clinical Global Impression Scale by a physician. |
| Morgan et al. (2013) | People seeking treatment for tobacco smoking (n=24) | Inhaler use, as needed, 400 μg administered in each depression of the inhaler | CBD (STI Pharmaceutical) dissolved in absolute ethanol ~5% | Randomized, double-blind, placebo-controlled | CBD decreased tobacco smoking by 40% |
| Morgan et al. (2018) | Light cannabis users (n=24) | 16 mg, inhaled (vaporized) | CBD (STI Pharmaceuticals) dissolved in alcohol | Randomized, double-blind, placebo-controlled | CBD inhibited THC (8 mg, vaporized) - induced increases on the Psychomimetic State Inventory |

| Reference | Study Sample | CBD Dose, and Route | Drug Formulation | Study Details | Summary Outcomes |
|---|---|---|---|---|---|
| Solowij et al. (2019) | Current cannabis users and non-naive non-users (n=36) | 4 or 400 mg inhaled (vaporized) | CBD (STI Pharmaceuticals) dissolved in ethanol (10% solution) | Randomized, double-blind, placebo-controlled | CBD-THC combinations with relatively high CBD (400 mg) were less intoxicating than THC alone, however, when the CBD dose was reduced to 4 mg it increased THC-induced intoxication |
| Zuardi et al. (2017) | Healthy adults (n=60) | 100, 300, or 900 mg, p.o. | Gelatin capsule containing 9.6% pure CBD dissolved in corn oil | Randomized, double-blind, placebo-controlled | 300 mg (but not 100 or 900 mg) reduced subjective ratings of anxiety. |
| Zuardi et al. (1993) | Healthy adults (n=40) | 300 mg, p.o. | Gelatin capsule containing CBD (from Dr. R. Mechoulam) dissolved in corn oil | Randomized, double-blind, placebo-controlled | CBD decreased anxiety after a simulated pubic speaking test. |