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KNOWLEDGE SYNTHESIS

Cannabidiol:
A Review of Its Safety for Human Consumption

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1. Executive Summary

Cannabidiol (CBD) is a non-psychoactive constituent of the cannabis plant that is increasingly available to the general public, either for medicinal use or as a nutritional supplement. The focus of this knowledge synthesis is to evaluate the peer-reviewed literature regarding the safety profile of short- and long-term CBD consumption using placebo-controlled studies in humans.

Pharmacologically, CBD is a highly lipophilic (fat-soluble) molecule with long half-life that is a negative allosteric modulator of the CB_1 receptor.

In pediatric trials of CBD for seizure disorders, high-doses of CBD (adult dose equivalents of 700 – 3500 mg/day) are significantly associated with minor adverse events (i.e., somnolence, decreased appetite and diarrhea). Notably, patients in these trials are medically complex and typically receiving a number of concomitant medications, and adverse events may be the result of drug interaction.

In adults, a sizable number of studies using acute administration of doses up to 1280 mg/day suggest minimal adverse effects. Similarly, studies of adults using CBD for long time-periods reveal minimal adverse effects.

CBD interacts with a number of members of the cytochrome p450 enzyme family, inhibiting CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5. High doses have been shown to have drug interactions with clobazam, which is metabolized via CYP2C19. Other interactions between CBD and drugs metabolized via these enzymes are hypothesized but have not been empirically demonstrated.

Collectively, the evidence suggests that low-dose CBD ($\leq$200 mg/day) is associated with minimal risk in otherwise healthy adults.

High (clinical) doses (>1000 mg/day for adults) do have a meaningful side-effect profile, including somnolence and diarrhea. A greater risk of drug interactions is also present for individuals receiving high doses.

2. Introduction

Cannabidiol (CBD) is a chemically active molecule derived from the cannabis plant. It was first isolated in 1940, and chemically described in 1963 (Adams, Hunt, & Clark, 1940; R Mechoulam & Shvo, 1963; A. W. Zuardi, 2008). Clinically, CBD has antiseizure activity and is moderately effective for reducing seizure frequency and severity associated with some forms of epilepsy (O Devinsky et al., 2017; Orrin Devinsky et al., 2016; Orrin Devinsky, Patel, Cross, et al., 2018). More preliminary evidence suggests that CBD may have a therapeutic role in the management of pain, inflammatory disorders, neurological conditions such as multiple sclerosis and Parkinson's disease, as well psychiatric conditions such as post-traumatic stress disorder, anxiety, depression, alcohol use disorder and psychosis (Bhattacharyya et al., 2010; Borgwardt et al., 2008; Fusar-Poli et al., 2009; Philpott, O'Brien, & McDougall, 2017; E. Russo & Guy, 2005; Turna et al., 2019; A. W. Zuardi, 2008; A. W. Zuardi et al., 2009). CBD is markedly different from the other most commonly studied cannabinoid, Δ-9-tetrahydrocannabinol (THC), in that it does not have psychoactive effects and is generally considered safe across a wide dose range (Expert Committee on Drug Dependence, 2017). Nonetheless, it is a biologically active compound that is increasingly commercially available to the general public, either for medicinal use or as a nutritional supplement (Owram, 2019). Therefore, the focus of this knowledge synthesis is to evaluate the peer-reviewed literature regarding the safety profile of short- and long-term CBD consumption in humans.

2. Pharmacology and Pharmacokinetics

2.1 Structure and Site of Action

CBD is a small two ring molecule, and its shape and structure are similar to that of THC (ElSohly & Slade, 2005). The key difference between both molecules however, differs in that the second ring of THC is closed, whereas in CBD it is open (Fig. 1)(Nahler, Grotenhermen, Zuardi, & Crippa, 2017). In strongly acidic environments (e.g. hydrochloric acid) it is possible for the molecule to convert from CBD to THC (R Mechoulam & Shvo, 1963; Merrick et al., 2016).

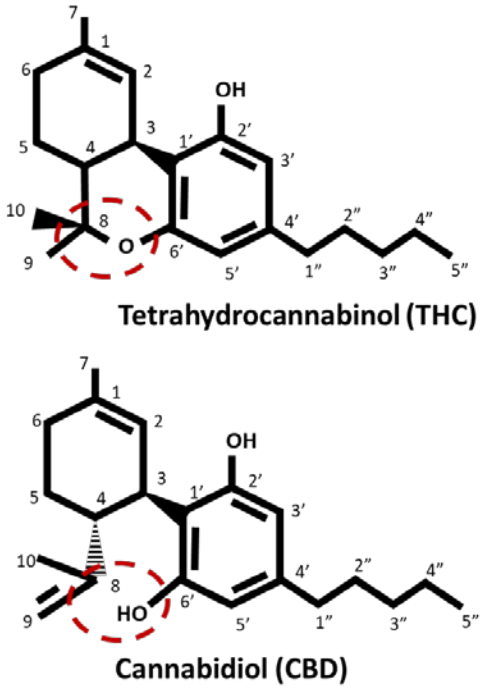


Figure 1. Structural Similarity Between CBD and THC

CBD is known to act at similar receptors as THC such as CB_1 and CB_2 (Laprairie, Bagher, & Kelly, 2015; Morales, Reggio, & Jagerovic, 2017; Tham et al., 2018). THC acts as a positive orthosteric modulator of the CB_1 receptor, which in turn results in psychotropic effects. In contrast, CBD is a negative allosteric modulator of the CB_1 receptor. As a result, CBD does not stimulate psychotropic effects associated with THC such as euphoria, perceptual changes in the senses, altered mood, somnolence, or cognitive impairment (Morales et al., 2017). Additionally CBD has been shown to interact with several other receptors which may be involved with inflammation, metabolism, regulation of mood, the immune system, memory, and pain (Bakas et al., 2017; Brown, Laun, & Song, 2017; Campa, Linge, Jim, & Pilar-cu, 2016; Elena, Franco, & Aymerich, 2017; Gomes et al., 2015; Gonca & Darıcı, 2015; Hegde et al., 2015; Hind, England, & Sullivan, 2016; Katsidoni, Anagnostou, & Panagis, 2012; Laprairie et al., 2015; Laun, Shrader, Brown, & Song, 2018; Mahgoub et al., 2013; Martínez-pinilla et al., 2017; Morales, Goya, Jagerovic, & Hernandez-folgado, 2016; Nabissi et al., 2015; Sonego, Gomes, Del, & Guimaraes, 2016; Tham et al., 2018).

2.2 Synthesis

The biosynthesis of CBD involves many steps, and begins with the formation of cannabigerolic acid (CBGA), which, after exposure to CBGA synthase becomes cannabidiolic acid (CBDA) (Lewis, Yang, Wasilewski, Clarke, & Kotra, 2017; E. B. Russo, 2017). Either through exposure to heat, or over large periods of time, a carboxylic acid group is removed from CBDA to yield CBD (Fig. 2) (Lewis et al., 2017; E. B. Russo, 2017). The quantity of CBD produced is contingent upon the amount of CBGA and the activity of CBDA synthase in a cannabis plant, as well as the amount of heat applied to CBDA (Lewis et al., 2017; E. B. Russo, 2017). Heat may be derived through combustion (as in smoking), or through a vaporizer (Grotenhermen, 2003; Lanz, Mattsson, Soydaner, & Brenneisen, 2016; Lewis et al., 2017). In the case of concentrated oils, CBDA is converted to CBD in industrial heated ovens (Lewis et al., 2017). CBD can also be created synthetically, although this is not a common method of production (Raphael Mechoulam, Parker, & Gallily, 2002).

2.3 Absorption and Distribution

CBD is a highly lipophilic (fat-soluble) molecule whose absorption can be influenced by the presence of other fatty foods at the time of consumption. In a recent study of young healthy adults who were given a single dose of 1,500 mg of CBD in a fasting state and with a high fat meal, researchers determined there was a 4.2-fold increase in the amount of CBD absorbed (AUC_t) in those that ate a high fat meal (Taylor, Gidal, Blakey, Tayo, & Morrison, 2018). Additionally, the maximum serum concentration (C_{max}) in subjects also increased 4.85-fold with a high fat meal (Taylor et al., 2018). Despite these increases in C_{max} and AUC_t, the time to reach maximum CBD concentration (T_{max}) was 4-5 hours, with or without food (Taylor et al., 2018). These findings are consistent with other studies assessing the impact of high fat food intake and concurrent CBD administration (GW Biosciences, 2018).

Once absorbed, CBD is distributed to the liver and fatty tissues, including brain tissue. As a result of its distribution to many tissues in the body, the half-life (t½) of CBD is long in comparison to other drugs and ranges from 41-113 hours after chronic daily administration. With a prolonged half-life, the influence of CBD systemically is also protracted, which has implications for interactions with other drugs consumed subsequently (Gaston, Bebin, Cutter, Liu, & Szaflarski, 2017; Geffrey, Pollack, Bruno, & Thiele, 2015; Grayson, Vines, Nichol, & Szaflarski, 2018; Leino et al., 2019).

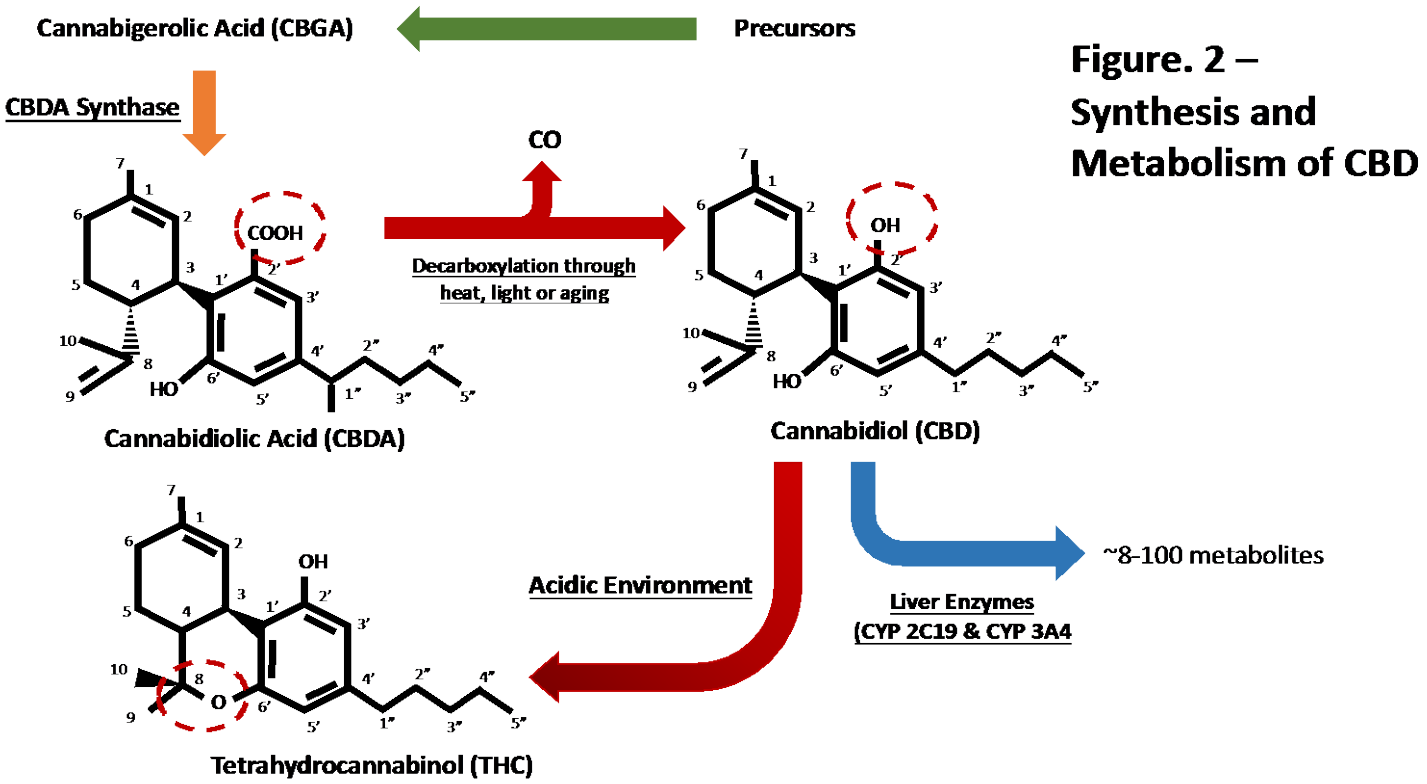


Figure. 2 – Synthesis and Metabolism of CBD

2.4 Metabolism and Excretion

Like most drugs, CBD undergoes metabolism in two phases in the liver. The first phase is responsible for adding small chemical groups, changing the polarity of the parent compound, which typically makes the compound inactive (Katzung, 2007). The second phase of metabolism is responsible for

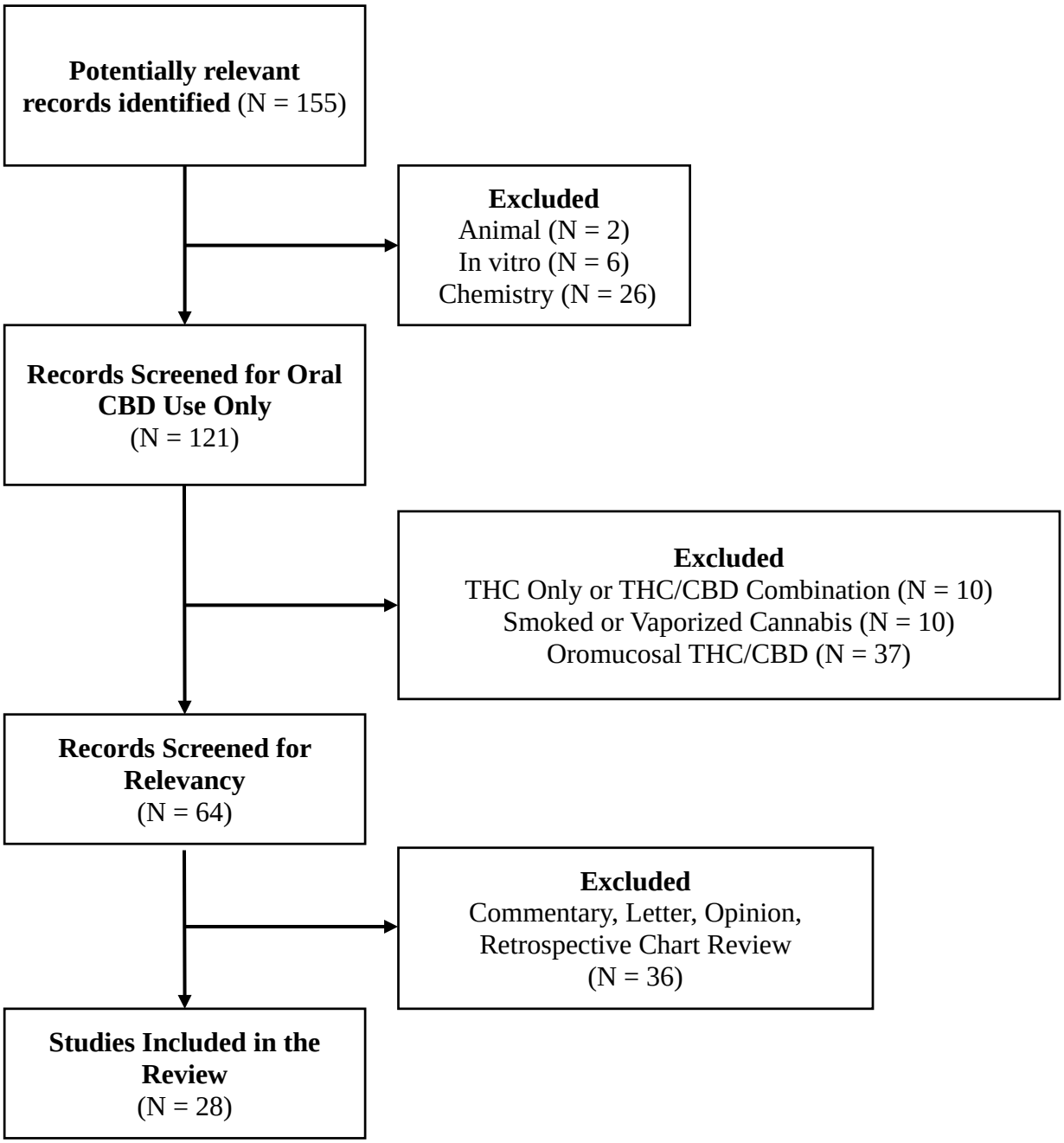
increasing the bulk of the compound for eventual excretion (Katzung, 2007). The first phase is carried out by the cytochrome p450 family of enzymes, which introduce small but significant changes to drug molecules, such as CBD, forming metabolites that may be active or inactive. The main enzyme responsible for CBD metabolism is CYP2C19, which metabolizes CBD primarily to 7-COOH-CBD and 7-OH-CBD (Fig. 2), both of which are known to have clinical activity and the latter of which primarily has antiseizure activity (Jiang, Yamaori, Takeda, Yamamoto, & Watanabe, 2011). In addition to CYP2C19, another enzyme, CYP3A4 is largely responsible for forming other minor metabolites. While only 8 metabolites have been found, some animal and human studies suggest the possibility of over 100 CBD metabolites, with unknown systemic activity (Fig. 2) (Harvey, 1991; Ujváry & Hanuš, 2016). After undergoing changes with cytochrome enzymes, in a second phase, enzymes known as UDP-glucuronosyltransferases, are responsible for increasing the bulk of CBD metabolites for excretion (Mazur et al., 2009). CBD and its metabolites are eliminated from the body unchanged in urine (16%) and to a larger extent in feces (33%) after a period of up to 72 hours after administration (Ohlsson et al., 1986).

4. Safety Review

In order to assess the safety of CBD in humans, we conducted a literature search (Appendix I) and review. The research designs that most directly address the issue of safety for human consumption are placebo-controlled studies in humans, which were the primary focus. Clinical trials and experimental studies investigating CBD alone, with another medication, or in comparison to placebo were included. However, studies assessing a preparation containing both CBD and THC were excluded so as to avoid confounding via adverse events from THC. We defined a minor adverse event as a common, non-life threatening event resulting in minor and reversible injury, not requiring hospitalization, and which may have required discontinuation of a study drug. A major life-threatening event was defined as requiring hospitalization, and/or resulted in significant injury or death. We stratified our results according to

pediatric or adult populations. Studies using non-human animal models were considered beyond the scope of the current review. Our literature search identified 155 citations, of which 28 were eligible for review (Figure 1).

Figure 1: Flow Diagram of Study Selection



4.1 Dosing Range and Adverse Events

4.1.1 Pediatric Trials

CBD has been assessed in several well-designed controlled clinical trials and long-term follow-up studies in pediatric populations. The first trial by Devinsky et al. published in 2016, was designed to study whether CBD was safe and effective as an add on treatment with other anti-epileptic drugs for pediatric patients (Orrin Devinsky et al., 2016). This study was open label with no placebo group comparison, and CBD was dosed by weight ranging from 25-50 mg/kg/day (Orrin Devinsky et al., 2016). For adult context, in a 70kg individual, this dosing reflects 1750 mg to 3500 mg per day. After 12 weeks patients reported significant reduction in the number of seizures per month, but also a substantial number reported side effects. Most commonly patients reported increased somnolence, changes in appetite, diarrhea, fatigue/lethargy and it was also noted that liver enzymes were also elevated in several patients taking valproic acid for their epilepsy treatment (see Table 1 for event rates) (Orrin Devinsky et al., 2016).

Two randomized, placebo-controlled trials were conducted by Devinksy et al. and published in 2017 and 2018 (O Devinsky et al., 2017). In the 2017 trial, children with treatment-resistant epilepsy were randomized to receive either 10 mg/kg/day of CBD, or placebo, for up to 14 weeks (O Devinsky et al., 2017). For adult context, in a 70kg individual, this dosing reflects 700 mg. Participants reported significant reduction in seizures, however in comparison to placebo, patients taking CBD reported marked increases in adverse events including somnolence, decreased appetite, diarrhea, fatigue, lethargy, vomiting, and convulsions (Table 1) (O Devinsky et al., 2017). In the 2018 trial, children with treatment resistant epilepsy were given either CBD 10 mg/kg/day, CBD 20 mg/kg/day or placebo for 14 weeks (Orrin Devinsky, Patel, Thiele, et al., 2018). Adverse event rates were greater in CBD

treatment groups as compared to placebo, in particular for somnolence, decreased appetite and diarrhea (Table 1). Additionally, higher event rates for these adverse effects showed a dose response relationship. Lastly, in the most recent study conducted on CBD in pediatric epilepsy disorders, patients received either CBD 20 mg/kg/day or placebo for 14 weeks, in addition to their standard antiepileptic medications (Thiele et al., 2018). Unlike in previous trials where adverse events were not distinguished causal factors, researchers analyzed adverse events that were treatment related, reporting a noticeably lower event rate for somnolence and decreased appetite, as compared to previous trials (Table 1) (Thiele et al., 2018). Furthermore, the incidence of pyrexia was negligible and vomiting was largely no different than placebo, suggesting these effects are not due to CBD administration (Thiele et al., 2018).

A systematic review and meta-analysis analyzing the trials in Table 1, calculated the relative risks of use of CBD in comparison to placebo (Lattanzi et al., 2018). In pediatric populations suffering from epilepsy receiving CBD 10-50 mg/kg/day, the relative risk increase for somnolence, decreased appetite and diarrhea was 192%, 315% and 1727% respectively, which were all deemed statistically significant as compared to placebo (Lattanzi et al., 2018). From this data, the calculation of the absolute risk increase for somnolence, decreased appetite and diarrhea, was 16.1%, 15.3% and 15.2% respectively, when patients are exposed to CBD in comparison to placebo. To put this into context, the number of individuals required to have one significant adverse effect when exposed to CBD, such as somnolence, diarrhea, or decreased appetite is between 6 to 7.

Table 1 - Pediatric Multiple Dose Studies Assessing CBD Safety

(Orrin Devinsky et al., 2016)		(O Devinsky et al., 2017)			(Orrin Devinsky, Patel, Cross, et al., 2018)				(Thiele et al., 2018)		
Open label trial		RCT			RCT				RCT		
CBD 25 or 50 mg/kg/day for 12 weeks		CBD 20 mg/kg/day or placebo for 14 weeks			CBD 10 or CBD 20 mg/kg/day or Placebo for 14 weeks				CBD 20 mg/kg/day or placebo for 14 weeks		
N = 214		N = 120			N = 225				N = 171		
10.5 years		9.8 years			15.5 years				15.5 years		
Adverse Event	CBD	Adverse Event	CBD	Placebo	Adverse Event	CBD 10 mg/kg	CBD 20 mg/kg	Placebo	Treatment Related Adverse Event	CBD	Placebo
Somnolence	25%	Somnolence	36%	10%	Somnolence	21%	30%	5%	Diarrhea	13%	4%
Decreased Appetite	19%	Decreased Appetite	28%	5%	Decreased Appetite	16%	26%	8%	Somnolence	14%	8%
Diarrhea	19%	Diarrhea	31%	10%	Diarrhea	10%	15%	8%	Pyrexia	1%	1%
Fatigue Increased	13%	Fatigue	20%	3%	Upper Respiratory Tract Infection	16%	13%	14%	Decreased Appetite	9%	1%
Increased Appetite	9%	Lethargy	13%	5%	Pyrexia	9%	12%	16%	Vomiting	7%	5%
Lethargy	7%	Vomiting	15%	5%	Vomiting	6%	12%	12%			
Elevated liver enzymes	7%	Pyrexia	15%	8%	Mild nasopharyngitis	4%	11%	7%			
		Convulsion	11%	5%	Status Epilepticus	10%	5%	4%			
		Upper Respiratory Tract Infection	11%	8%							

4.1.2 Adult Trials

Studies in adults assessing CBD alone (without the presence of THC) are substantially constrained by small samples sizes, and short duration of exposure (Table 2). Studies included in Table 2 were designed to ascertain the potential role of CBD in the treatment of a variety of conditions and its mechanistic effects but were not designed to fully assess adverse event rates. These studies used doses up to 1280 mg and did not reveal meaningful levels of adverse events of CBD.

Table 2 – Cannabis Studies Evaluating the Safety and Efficacy of CBD for Medicinal Use

Reference	Trial Design	Subjects	Clinical Question	CBD Intervention	Comparator Treatment	Protocol	Effects Associated with CBD
(Babalonis et al., 2017)	RCT	n = 31 Male = 14/31 Age(mean) = 29.1 years Comorbidities - None	Does CBD in combination with THC increase abuse liability?	Single dose CBD 0 mg, 200 mg, 400 mg, 800 mg or corresponding placebo	Smoked Dried Cannabis – 5.3-5.8% THC, 0.01% CBD	Administered oral CBD or Placebo as a single dose along with smoking cannabis for one session	Regardless of dose, no abuse liability or psychoactive effects noted
(Bhattacharyya et al., 2010)	Observational Trial	N = 15 Male = 15/15 Age (mean) = 26.7 Comorbidities = none	Does CBD differ from THC in regional brain function?	CBD 600 mg as a single oral dose	Placebo or THC 10 mg	Administered oral CBD, THC, or Placebo to blinded participants on three separate sessions, sequence randomized, and fMRI performed after each intervention	THC and CBD had opposite effects on verbal recall, response inhibition, amygdala activation to fearful faces, speech recognition and visual processing.
(J. A. Crippa et al., 2004)	Observational Trial	N = 10 Male = 10/10 Age = 29.8 Comorbidities = none	Does CBD affect neural activity in areas that normally mediate anxiety?	CBD 400 mg as a single oral dose	Placebo	Administered CBD in one session or placebo to 5 patients each, and repeated procedure following week. Analyzed regional cerebral blood flow 2 hours post treatment.	Decreased uptake of marker in brain regions associated with anxiety when CBD was administered.
(J. A. S. Crippa et al., 2011)	Observational Trial	N = 10 Male = 10/10 Age = 24.2 Comorbidities = Generalized SAD	Does CBD modulate the neurophysiology of individuals with SAD?	CBD 400 mg as a single oral dose	Placebo	Administered CBD in one session or placebo to 5 patients each, and repeated procedure following week. Analyzed regional cerebral blood flow 2 hours post treatment as well as SAD with the BSPS.	CBD reduced significantly social anxiety, and reduced marker uptake in regions associated with social anxiety (limbic and paralimbic brain areas.)

(Fusar-Poli et al., 2009)	Observational Trial	N = 15 Male = 15/15 Comorbidities = healthy subjects	Does CBD or THC have different effects on regional brain function during emotional processing?	CBD 600 mg	Placebo or THC 10 mg	Administered oral CBD, THC, or Placebo to blinded participants on three separate sessions, sequence randomized, and fMRI performed after each intervention.	THC and CBD had different effects on neural, electrodermal and symptomatic responses to fearful faces. CBD may reduce autonomic arousal and subjective anxiety whereas THC mainly served as anxiogenic.
(Englund et al., 2013)	Randomized trial	N = 48 Male = 27/48 Age (mean) = 25-26 years Comorbidities = healthy subjects	Does pre-treatment with pure CBD inhibit THC elicited psychosis?	CBD 600 mg as a single oral dose	Placebo IV THC (1.5 mg)	Participants randomly allocated to placebo or CBD groups under double blind conditions. Measurements baseline (CEQ), after CBD or placebo administration and after IV THC administration. (CEQ, PANSS, SSPS, UMACL, HVLT-R) .	Clinically significant psychotic symptoms were less likely in the CBD group compared to placebo, and a statistically non-significant reduction in PANSS scores was noted. Post-THC paranoia was less in the CBD groups (SSPS). Episodic memory was also found to be poorer in the placebo group vs. placebo.
(Gong, Tashkin, Simmons, Calvarese, & Shapiro, 1984)	Randomized Trial	N = 59 Male = 59/59 Age = 21-32 years of age Comorbidities = healthy subjects	Do cannabinoids produce a bronchodilator effect?	CBD 100 mg, 600 mg or 1200 mg as a single dose	Delta-9-THC 20 mg, Delta-8-THC 50 mg and 75 mg CBN 100 mg 600 mg and 1200 mg Placebo	Dose response study – 18 subjects received each of the following in the CBD intervention and comparator treatments as single doses and BP, HR, RR airway conductance and airway resistance was measured.	CBD 1200 mg did not induce significant dose-related physiologic effects in experiences cannabis users. CBD when combined with THC did not induce significant bronchodilation but did exert effects on heart rates and subjective feelings of being "high." CBD was not associated with a bronchodilator effect, whereas THC had mild bronchodilator effects.
				CBD 1200 mg	Delta-9-THC 10 mg CBN 600 mg Delta-9-THC 5 mg and CBN 400 mg Delta-9-THC 5 mg and CBD 400 mg Placebo	Interaction study – 12 subjects received each of the following in the CBD intervention and comparator treatments in 24-48 hour intervals. Measurements	

						and analysis were the same as the dose response study.	
				CBD 600 mg CBD 1200 mg	CBN 600 mg Delta-9-THC 20 mg Placebo	Subacute study – 29 subjects received one of the following drugs in the morning for 20 consecutive days in a double blinded, randomized fashion. Measurements taken on days 5, 12, 19.	
(Haney et al., 2016)	RCT	n = 31 Male = 14/31 Age(mean) = 29.1 years Comorbidities - None	Does CBD influence the effects of smoking cannabis (reinforcing, subjective, cognitive and physiological effects.)?	Single dose CBD 0 mg, 200 mg, 400 mg, 800 mg or corresponding placebo	Smoked Dried Cannabis – 5.3-5.8% THC, 0.01% CBD	Administered oral CBD or Placebo as a single dose along with smoking cannabis for one session and the behavioural and cardiovascular effects of cannabis was measured throughout the session.	CBD was shown not to reduce the reinforcing, physiological or positive subjective effects of smoked cannabis.
(Leweke, Schneider, Radwan, Schmidt, & Emrich, 2000)	Observational Trial	N = 9 Male 9/9 Age = 29.4 years Comorbidities = healthy subjects	Is binocular depth inversion present when individuals are exposed to CBD?	CBD 200 mg as a single dose	Placebo and Nabilone 1 mg as single doses	On the first day of the study, each participant received CBD 200 mg and placebo, the second day of the study CBD 200 mg and nabilone 1 mg, and the third day of the study nabilone 1 mg and placebo. Binocular depth inversion was tested after each dose administration.	CBD did not produce binocular depth inversion, while THC did. The combination of CBD with THC resulted in less binocular depth inversion.
(Manini et al., 2015)	Double blinded, placebo controlled cross-over study	N = 17 Male = 38.5% Age = Not reported, age range 21-65 years Comorbidities = healthy subjects	Is CBD safe to administer to individuals on high potency opioids, and does the pharmacokinetics of opioids change in the presence of CBD?	CBD 400 mg or 800 mg orally as a single dose, and repeated at a second session	Placebo as a single dose, and repeated at a second session	Individuals were blinded to receive either placebo, CBD 400 mg or CBD 800 mg in one session in which they received 0.5 mcg/kg of fentanyl, and	CBD does not exacerbate adverse effects associated with IV fentanyl, and was safe and well tolerated.

						then one week later in which they received 1 mcg/kg of fentanyl. Blood sampling, SAFTEE assessment were performed at each session.	
(Winston-Brown et al., 2011)	Double blinded, placebo-controlled, pseudo-randomized within-subject study	N = 14 Male = 14/14 Age = 26.7 years Comorbidities = none	Does THC and CBD alter activation in the lateral temporal and occipital cortices during auditory and visual processing?	CBD 600 mg as a single dose	THC 10 mg and placebo	Before each fMRI scan, participants were given either 10 mg of THC, 600 mg of CBD or placebo. Subjects were asked to rate their subjective experiences at baseline, before scanning (1h), after scanning (2h) and 1 hour post scanning (3h).	CBD had no anxious, intoxicating or positive psychotic effects as opposed to THC. CBD was associated with activation in the right temporal cortex during auditory processing, and THC vs. CBD had opposing effects in the right posterior superior temporal gyrus, right-sided homolog to Wernicke's area.
(A. W. Zuardi et al., 2009)	Open-label trial	N = 6 Male = 4/6 Age = 58.8 Comorbidities = Parkinson's disease and previous symptoms of psychosis	Is CBD safe and effective as a treatment for psychotic symptoms in Parkinson's disease?	CBD dosed at 150 mg in week 1, increase to 250 mg in week 2, 325 mg in week 3 and lastly to 400 mg in week 4.	No corresponding placebo	Patients were administered CBD in escalating doses over a 4 week period, and the BPRS, PPQ, UPDRS, and CGI-I were administered at each week.	Statistically significant reductions in BPRS, PPQ, UPDRS, and CGI-I scores.
(A. W. Zuardi et al., 2010)	Case Series	N = 2 Male = 0/2 Age (mean) = 35.5 years Comorbidities = Bipolar Affective Disorder	What is the safety and efficacy of CBD for Bipolar Affective Disorder?	CBD 600 mg once daily which was increased to CBD 900 mg once daily and to a maximum of 1200 mg per day over 25 day period	Placebo Olanzapine 10-15 mg per day	Patients were administered CBD 600 mg per day which was increased to 1200 mg per day over a 25 day period. During the first 14 days, Olanzapine 10-15 mg was provided and then withdrawn to study the effects of CBD alone for mania.	The YMRS and BPRS scores were reduced by 37% and 31% respectively with the Olanzapine and CBD combination, but no additional improvement was noted on CBD monotherapy. CBD was not effective for BAD symptom management, however was not associated with any adverse effects.
(A. Zuardi et al., 2006)	Case Series	N = 3 Male = 3/3 Age = 22.7 years Comorbidities = treatment	Is CBD effective as a monotherapy treatment for treatment resistant schizophrenia?	Given CBD 40 mg/day at initiation and dose double every 5 days until reaching a maximum of 1280	Placebo given at the first 5 days of the study, and on day Day 35 for a 5 day period. Placebo was	Patients were administered CBD in an inpatient setting, after receiving	Case 1 showed improvements in symptoms, and worsened once placebo was given. Case 2 showed no

		resistant schizophrenia		mg per day.	discontinued and olanzapine was started at day 40.	placebo for 5 days. The dose of CBD started at 40 mg per day, and doubled every 5 days until a maximum of 1280 mg reached by day 35. Days 35-40 placebo was given, and Days 41-55 Olanzapine was given. BPRS was administered on days 5, 35, 40, and 55.	improvement with CBD. Case 3 showed minimal improvement with CBD for positive and negative symptoms.

Studies included in Tables 3 and 4 were of longer duration than those in Table 2, and were designed to measure adverse effect profiles and are reviewed more extensively in this review. The first such study was conducted in 1991 among 15 patients with Huntington's disease. Participants were randomized to receive either CBD at a dose of 10 mg/kg/day or placebo for 7 days, went through a washout the 8th day, and then crossed over and received CBD or placebo for an additional 7 days. (P. Consroe et al., 1991) The average weight of participants was 67.9 kg, translating into an average dose of CBD administered to patients was 679 mg per patient per day. Adverse effects were not reported individually, rather by the average number of adverse events, per patient, during the treatment period. Participants reported a mean average of 5.3 side effects with CBD vs. 5.2 with placebo, which was a statistically nonsignificant finding (p=0.98). (P. Consroe et al., 1991) Mean blood pressure, pulse rate and body weight were monitored during CBD and placebo treatment, with no statistically significant differences between treatments. (P. Consroe et al., 1991) As noted, a significant limitation of this study was that it was underpowered due to small sample size. Additionally, the washout period was truncated, as it takes approximately 4-5 days for CBD to be eliminated systemically. It is likely that patients receiving placebo treatment after CBD would have continued effects from exposure to CBD,

thereby increasing the likelihood that similar rates of side effects were reported in both groups. These design issues notwithstanding, the study did not reveal meaningful levels of adverse events.

A 2017 study randomized 19 patients with Crohn's disease to receive either placebo or CBD 20 mg per day for a total of 8 weeks. (Naftali et al., 2017a) CBD was obtained from the cannabis plant and purified to 99.5% and dissolved in olive oil and administered as a liquid dosage form. After the treatment period, no differences between groups were found in blood counts, liver or kidney function tests. Additionally, rates of side effects such as headache, sleepiness, nausea and dizziness between groups were very similar between groups. Researchers reported that CBD at a dose of 20 mg was safe, with no statistically or clinically significant harms associated with use among their participants. (Naftali et al., 2017a) Due to the small sample size in this study, it may have also been underpowered to detect differences between CBD and placebo.

A larger randomized control trial conducted in 88 patients suffering from schizophrenia was conducted to assess the efficacy and safety of CBD as an antipsychotic (Mcguire et al., 2018). Participants were randomized to receive either CBD 1,000 mg or placebo for a duration of 6 weeks. Participants receiving CBD demonstrated improvements in symptoms and function but were more likely to suffer from a gastrointestinal related adverse effect than participants receiving placebo (Mcguire et al., 2018). There were slight increases in the incidence of metabolic, nutritional, skin and subcutaneous disorders among patients receiving CBD but due to the marginal differences between CBD and placebo, these may not be clinically meaningful (Mcguire et al., 2018).

Table 3 - Adult Multiple Dose Studies Assessing CBD Safety

	(P. Consroe et al., 1991)	**(Naftali et al., 2017b)**			**(Mcguire et al., 2018)**		
Design	Cross Over RCT	RCT			RCT		
Dose	10 mg/kg/day for 7 days Placebo for 7 days	20 mg/kg/day or placebo for 8 weeks			1,000 mg/day or placebo for 6 weeks		
Number of Participants	N = 15	N = 19			N = 88		
Age (mean)	52 years	Placebo group (32 years) CBD Group (45 years)			41 years		
Adverse Events	Rare and minor elevations in complete blood count values liver function tests. Difference between number of cannabis related side effects, blood pressure, pulse rate and body weight were non significant.	**Adverse Effect$^{\Omega}$**	**CBD$^{\Psi}$**	**Placebo**	**Difference**	**Treatment Related Adverse Event**	**CBD**	**Placebo**
		Headache	1.2	1.4	Not significant	Gastrointestinal Disorders	18.6%	6.7%
		Sleepiness	3.8	3.6	Not significant	Nervous System Disorders	4.7%	8.9%
		Nausea	2.8	3.5	Not significant	Psychiatric Disorders	2.3%	6.7%
		Dizziness	1.7	2	Not significant	Metabolism and Nutrition Disorders	4.7%	2.2%
		Ω Not defined as treatment related adverse effects **Ψ** values were ranked on a scale of 1-7				Skin and Subcutaneous Tissue Disorders	4.7%	2.2%

A pharmacokinetic study in 2018 aimed to address the effect of single high doses and multiple high doses, as well as food, on the rates of adverse effects. In the first arm, 32 healthy subjects were either given a single dose of CBD 1,500 mg, 3,000 mg, 4,500 mg and 6,000 mg or placebo and were asked to report adverse effects immediately following each single dose given (Taylor et al., 2018). Compared to placebo, rates of any adverse effect were similar. Additionally, rates of gastrointestinal and nervous system disorders did not differ compared to placebo. In the second arm, 24 healthy participants were either given multiple doses of CBD as 750 mg twice daily for one week, 1,500 mg twice daily for one week or placebo and were asked to report adverse effects. Rates of diarrhea, nausea, dizziness, feeling cold, rash, and insomnia were greater with CBD use and showed a positive dose dependent relationship (Table 4) (Taylor et al., 2018). For example, at doses of 750 mg, incidence of diarrhea and nausea were 44.4% and 33.3%, respectively. In comparison, at doses of 1,500 mg, the incidence of diarrhea

increased to 88.9% and nausea 55.5%. Additionally, the occurrences of dizziness, rash, somnolence and feeling cold were only documented at a higher dose of 1,500 mg, and not at a lower dose of 750 mg. In the third arm, a single dose of 1,500 mg of CBD was given to 12 participants in a fasting state, and another 12 participants were given the same dose in fed state (after a high fat meal). After a high fat meal, participants reported higher rates of nausea, abdominal discomfort, headache, somnolence and nasopharyngitis (Table 4). (Taylor et al., 2018) In this study, differences were noted amongst placebo and treatment groups, despite small sample sizes. Additionally, doses were generally much higher than previously studied and prescribed in practice, which may explain the increased prevalence of side effects among participants. The study designated all side effects as mild in severity.

<table>
<tr><th colspan="8">Table 4 –High Dose CBD Safety Analyses (Taylor et al., 2018)</th></tr>
<tr><td></td><td>1st arm</td><td colspan="4">2nd arm</td><td colspan="2">3rd arm</td></tr>
<tr><td>Design</td><td colspan="7">Open label trial</td></tr>
<tr><td>Dose</td><td>Single dose of 1,500 mg, 3,000 mg, 4,500 mg or 6,000 mg compared to placebo</td><td colspan="4">Multiple dose of 750 mg twice daily or 1,500 mg compared to placebo for 7 days</td><td colspan="2">Single dose of 1,500 mg in a fasted state or after a high fat meal</td></tr>
<tr><td>Number of Participants</td><td>N = 32</td><td colspan="4">N = 24</td><td colspan="2">N = 24</td></tr>
<tr><td rowspan="9">Adverse Events</td><td rowspan="9">No dose related differences in diarrhea, abdominal pain, diarrhea, nausea, somnolence, headache, dizziness, disturbance in attention</td><td>Adverse Effect</td><td>Placebo</td><td>750mg</td><td>1500mg</td><td>Adverse Effect</td><td>Fasted</td><td>Fed</td></tr>
<tr><td>Diarrhea</td><td>0%</td><td>44.4%</td><td>88.9%</td><td>Nausea</td><td>0%</td><td>33.3%</td></tr>
<tr><td>Nausea</td><td>16.7%</td><td>33.3%</td><td>55.6%</td><td>Abdominal Discomfort</td><td>0%</td><td>16.7%</td></tr>
<tr><td>Abdominal Pain</td><td>0%</td><td>22.2%</td><td>22.2%</td><td>Headache</td><td>8.3%</td><td>33.3%</td></tr>
<tr><td>Headache</td><td>0%</td><td>44.4%</td><td>44.4%</td><td>Somnolence</td><td>8.3%</td><td>25%</td></tr>
<tr><td>Dizziness</td><td>0%</td><td>0%</td><td>33.3%</td><td>Nasopharyngitis</td><td>0%</td><td>16.7%</td></tr>
<tr><td>Feeling Cold</td><td>0%</td><td>0%</td><td>22.2%</td><td colspan="3" rowspan="3"></td></tr>
<tr><td>Rash</td><td>0%</td><td>0%</td><td>22.2%</td></tr>
<tr><td>Insomnia</td><td>0%</td><td>0%</td><td>22.2%</td></tr>
</table>

4.2 Drug Interactions

Drug interactions represent a challenging issue for clinicians, in particular when patients are on many drugs as the number of potential clinically significant drug interactions increase exponentially (Marengoni & Onder, 2015). Most drug interactions occur during metabolism in liver microsomes, after the drug has been absorbed from the stomach. The drug responsible for the interaction typically inhibits or induces enzymes of the cytochrome p450 enzyme system, which subsequently alters the concentration of other drugs metabolized by these enzymes. (Katzung, 2007) The induction or inhibition of cytochrome p450 enzymes is a dose-dependent phenomenon, and may either follow a

predictable linear pattern (e.g. for every 25% increase in concentration of offending drug results in 25% reduction in drug metabolizing activity), or in a non-linear pattern (Katzung, 2007; Marengoni & Onder, 2015)

CBD interacts with more members of the cytochrome p450 enzyme family than THC (Table 5), and is proven to an inhibitor of CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5.(Okamoto, Watanabe, Jiang, Yamamoto, & Yamaori, 2013; S Yamaori, Okamoto, Yamamoto, & Watanabe, 2011; Satoshi Yamaori, Ebisawa, Okushima, Yamamoto, & Watanabe, 2011; Satoshi Yamaori, Hada, et al., 2011) Additionally, studies conducted by GW Pharma, the manufacturers of pharmaceutical drug Epidiolex® (Cannabidiol solution, indicated for use in pediatric epilepsy), have identified that CBD may be an inhibitor or inducer of CYP 1A2 and 2B6. To date, the implications of such cytochrome p450 enzyme effects have been reviewed in the context of cancer and epilepsy drug therapy, as CBD is commonly used for these conditions.

4.2.1 Antiseizure Drug Interactions

An open label study conducted in 81 adult and pediatric patients with epilepsy, and using other antiepileptic medication, administered a daily dose of 5mg/kg/day of CBD that increased to 50 mg/kg/day over a period of 20 weeks (Gaston et al., 2017). For example, in a 70 kg individuals, the initial CBD dose would be 350 mg and titrated up to a maximum of 3,500 mg per day. Researchers observed a clinically significant increase in levels of several drugs in patients, with most observed changes within normal range except for one anti-epileptic, clobazam, and its metabolite N-desmethylclobazam. Sedation was more frequent among individuals with high N-desmethylclobazam, and liver enzymes (AST and ALT) were higher in patients taking valproic acid (Gaston et al., 2017).

Researchers in this study suggested that the monitoring of serum drug levels and other lab values should be routine for individuals using CBD.

A study of 13 pediatric patients assessed effects of CBD on clobazam effectiveness and safety (Geffrey et al., 2015). After 8 weeks of CBD use (dose of 25 mg/kg/day), all patients reported a decrease in seizure frequency and increased sedation. On average, there was a 60% increase in Clobazam levels and a 500% increase in its metabolite, N-desmethylclobazam, which explained the increase in drug effectiveness, but also corresponding increase in sedation. Clinicians then decreased clobazam doses (this occurred 10 out of 13 patients in the study, by 10-90%), which retained the same efficacy but minimized sedation with CBD use (Geffrey et al., 2015). Researchers in this study also emphasized close drug monitoring of CBD and anti-epileptic drugs to adjust for drug interactions.

Another trial enrolled 78 healthy subjects, who were given CBD at a dose of 750 mg twice daily with either clobazam, stirpentol or valproic acid for an average of 4-8 weeks. Among participants receiving clobazam, levels of its metabolite N-Desmethylclobazam were increased, on average, by 240%. This drug interaction was mediated through direct inhibition of CYP2C19 by CBD. There were no increased reports of sedation among participants; however, 11.7% of subjects reported a rash, and 7.8% of individuals discontinued treatment due to adverse events. A list of potential drugs that may interact by CYP 2C19 enzyme inhibition are listed in Table 5.

Table 5 –Drugs Metabolized via CYP 2C19 That May Interact with CBD

Amitriptyline (Antidepressant)	Escitalopram (Antidepressant)	Phenobarbital (Anticonvulsant/Sedative)
Aripiprazole (Antipsychotic)	Fluoxetine (Antidepressant)	Phenytoin (Anticonvulsant)
Citalopram (Antidepressant)	Imipramine (Antidepressant)	Propranolol (Beta Blocker)
Clomipramine (Antidepressant)	Lansoprazole (PPI)	Progesterone (Hormone)
Clopidogrel (Anti-platelet)	Methadone (Analgesic)	Rabeprazole (PPI)
Clozapine (Antipsychotic)	Moclobemide (Antidepressant)	Sertraline (Antidepressant)
Cyclophosphamide (Chemotherapy)	Nortriptyline (Antidepressant)	Testosterone (Hormone)
Desipramine (Antidepressant)	Nelfiniavir (Antiviral)	Venlafaxine (Antidepressant)
Desogestrel (Hormone)	Olanzapine (Antipsychotic)	Voriconazole (Antidepressant)
Diazepam (Anticonvulsant/Hypnotic)	Omeprazole (PPI)	R-Warfarin (Anticoagulant)
Diphenhydramine (Antihistamine)	Pantoprazole (PPI)	
Doxepin (Antidepressant)		

PPI – Proton Pump Inhibitor

Adapted from (Desta, Zhao, Shin, & Flockhart, 2002; Horn & Hansten, 2008)

4.2.2 Cancer Chemotherapy Drug Interactions

A 2019 narrative review noted that CBD could potentially interact with chemotherapeutic agents from various drug classes including tyrosine kinase inhibitors, taxanes, vinca-alkaloids, topoisomerase inhibitors, alkylating agents, hormonal therapies and intercalants (Table 6) (Opitz, Ostroff, & Whitman, 2019). The authors suggested that such drug interactions could, in principle, alter the course of anticancer therapies, including the cancer cell resistance, metabolism of chemotherapeutic drugs, reduction or increase of side effects, or promotion of synergistic effects with chemotherapeutic agents (Opitz et al., 2019). Table 6 represents the potential drug interactions with CBD and chemotherapy drugs; however, there is no empirical evidence that CBD interacts with cancer chemotherapy drugs.

Table 6 – Potential Drug Interactions with Cancer Chemotherapy Drugs and CBD			
Drug Class	**Drug (Example)**	**Protein Involved**	**Effect on Protein**
Hormone	Tamoxifen	CYP 2D6 or 3A4	Inhibition of these proteins, resulting in subtherapeutic conversion of Tamoxifen to its active anticancer form.
Tyrosine Kinase Inhibitor	Imatinib	CYP 2C19 or 3A4	Inhibition, resulting in bioaccumulation of this drug increasing toxicity and adverse events such as edema, rash, numbness, nausea, vomiting, increased liver enzymes, increased susceptibility to infection and pain.
Alkylating Agent	Cyclophosphamide	CYP 2C19 or 3A4	
Taxane	Paclitaxel	CYP 3A4	
Adapted from: (Opitz et al., 2019)			

4.2.3 Case studies

Two case studies have reported possible interactions between CBD and other drugs. Tacrolimus is a drug routinely utilized to prevent rejection after transplant surgery as well as for treatment of autoimmune disorders. Tacrolimus drug levels are routinely monitored to prevent high serum levels, which are associated with nephrotoxicity and neurotoxicity. A single case report of a 32-year-old patient on Tacrolimus, who was given CBD at a dose of 2,000 mg per day for 10 days, as per study protocol in an epilepsy trial, resulting in decreased renal function (Leino et al., 2019). In order to manage this patient, the tacrolimus dose was held for several days and lowered and the patient's status normalized. After several weeks, a further increase in CBD dose to 2,900 mg was initiated to better manage seizures, which in turn resulted in renal dysfunction necessitating another dosage decrease in tacrolimus. As tacrolimus is metabolized by CYP3A4, it was inferred that CBD was inhibiting the metabolism of tacrolimus, resulting in renal toxicity (Leino et al., 2019).

In another case report, a 44-year-old on long term warfarin therapy to prevent stroke was placed on CBD 5 mg/kg/day to treat an underlying seizure disorder. His dose of CBD increased from 265 mg per day to 1800 mg per day over a 500 day period (Grayson et al., 2018). Prior to CBD initiation, his International Normalized Ratio (INR – a measurement used to monitor the effectiveness of anticoagulation and risk of bleeding with therapy) level was successfully stable for 6 months within the normal reference range of 2-3. However, after introduction of CBD, his INR fluctuated considerably between visits, with values regularly exceeding 3 and 4, necessitating a decrease in his Warfarin dose by several milligrams so as to avoid the risk of a serious bleed. Warfarin is mainly metabolized by CYP 3A4, but also CYP 1A2, CYP 2C9 and CYP2C19, therefore it was suggested that this interaction may have been due to inhibition of these enzymes by CBD.

5. Discussion

In the course of research into the effects of CBD on the human body over the past 40 years, evidence points to an overall wide margin of safety with use, with no reports of serious adverse events resulting in hospitalization or death (Bhattacharyya et al., 2010; Borgwardt et al., 2008; Paul Consroe, Kennedy, & Schram, 1991; O Devinsky et al., 2017; Orrin Devinsky et al., 2016; Orrin Devinsky, Patel, Thiele, et al., 2018; Fusar-Poli et al., 2009; Mcguire et al., 2018; Naftali et al., 2017b; Philpott et al., 2017; E. Russo & Guy, 2005; Taylor et al., 2018; Thiele et al., 2018; Turna et al., 2019; A. W. Zuardi, 2008; A. W. Zuardi et al., 2009). CBD has no abuse or dependence potential, and does not produce psychoactive effects in humans that are traditionally associated with Cannabis (and THC), such as alterations in mood, as well as motor and cognitive impairments (Table 1).

Nonetheless, CBD is biologically active and, at high doses, does have side effects. Based on the studies identified, a low dose of CBD for adults can be considered to be $\leq$200mg/day, a moderate dose can be considered to be >200mg - <1000mg/day, and a high dose can be considered >1000mg per day. In the

majority of randomized controlled trials conducted in pediatrics and in adults with high-dose CBD, ranging from 1,500 mg to 6,000 mg, the most common side effects were somnolence, fatigue, insomnia and to a lesser extent gastrointestinal disturbances, whereas with lower dose CBD (<100 mg/day) these side effects were not observed. The effects of high dose CBD on gastrointestinal side effects such as appetite suppression, nausea and diarrhea were under 20% in both adult and pediatric trials, which can be considered a dose limiting side effect albeit classified as minor and non-life-threatening in nature.

Of concern is the potential for CBD to interact with other drugs, potentially leading to clinically significant adverse effects. As previously discussed, CBD has both theoretical and clinically proven drug interaction potential, which could either enhance drug activity or cause increased side effects. This observation would be more pronounced in individuals receiving higher doses of CBD (>500 mg – 1,000 mg per day), over a prolonged period of time (>7 days) with concurrent use of drugs metabolized by CYP 2D6, 2C9, 2C19, 3A4. These enzymes are responsible for the metabolism of >50-70% of all known drugs, hence minor and major interaction effects could be seen with use of chronic high dose of CBD. Clinical management of the drug interaction effects would warrant reduction or discontinuation of CBD or the offending drug if the individual afflicted by the interaction were demonstrating intolerable symptoms. A more thorough exploration of the interaction effect of CBD on a variety of drug classes, including antibiotics, antiretrovirals, anticancer agents, anticoagulants, antiepileptics and antidepressant drug classes is warranted, as these drugs represent the most typical agents involved in clinically relevant drug interactions necessitating medical management. As most drug interactions observed appear to occur at higher doses, the lowest effective dosage of CBD for the shortest duration possible would be considered a conservative approach to mitigate interactions with another drug class. Consideration must be given to potential formulations of CBD in food or other health products, to limit the cumulative exposure to CBD beyond levels that can cause clinically significant drug interactions.

6. Conclusions

There is converging evidence that CBD is generally safe for human consumption in otherwise healthy individuals. It does not have psychoactive effects and or any reported adverse effects at low doses (e.g., ≤200 mg/day), or even high doses (e.g., >750 mg/day) when administered acutely. When used chronically for therapeutic purposes, its side effect profile is predominantly somnolence and GI disturbances. In spite of this wide margin of safety, gaps in the scientific literature remain present (e.g., long-term safety). As such, although the current evidence suggests that CBD is generally safe, ongoing surveillance and investigation remain warranted.

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Appendix I

Search Strategy

A pubmed search was conducted with the following keyword search terms “cannabidiol,” “mouth,” “oral.” Additional articles were identified through library search with the following additional terms “sleep,” “insomnia,” “epilepsy,” “drug interaction,” to yield a total of 155 articles for review. Articles accepted for review consisted of original research on oral dosage form of cannabidiol in humans. Results containing original research on combination CBD/THC oral products, Sativex® (oromucosal dosage form of THC and CBD), smoked or vaporized cannabis, animal studies, in vitro studies, cannabidiol chemistry, reviews, commentaries, letters and expert opinions were excluded.