CANNABIDIOL (CBD)

Critical Review Report

Expert Committee on Drug Dependence

Fortieth Meeting

Geneva, 4-7 June 2018

World Health Organization

Contents

Acknowledgements **4**

Summary **5**

1. Substance identification ***6***

A. International Nonproprietary Name (INN) *6*
B. Chemical Abstract Service (CAS) Registry Number *6*
C. Other Chemical Names *6*
D. Trade Names *6*
E. Street Names *6*
F. Physical Appearance *6*
G. WHO Review History *6*

2. Chemistry ***6***

A. Chemical Name *6*
B. Chemical Structure *7*
C. Stereoisomers *7*
D. Methods and Ease of Illicit Manufacturing *7*
E. Chemical Properties *9*
F. Identification and Analysis *9*

3. Ease of Convertibility Into Controlled Substances ***10***

4. General Pharmacology ***11***

A. Routes of administration and dosage *11*
B. Pharmacokinetics *11*
C. Pharmacodynamics *12*

5. Toxicology ***13***

6. Adverse Reactions in Humans ***13***

7. Dependence Potential ***14***

A. Animal Studies *14*
B. Human Studies *14*

8. Abuse Potential ***14***

A. Animal Studies *14*
B. Human Studies *14*

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use ***15***

10. Listing on the WHO Model List of Essential Medicines ***18***

11. Marketing Authorizations (as a Medicinal Product) ***18***

12. Industrial Use ***19***

13. Non-Medical Use, Abuse and Dependence ***20***

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence ***20***

15. Licit Production, Consumption and International Trade ***20***

16. Illicit Manufacture and Traffic and Related Information *20*

17. Current International Controls and Their Impact *20*

18. Current and Past National Controls *21*

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance *21*

References **22**

Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Department of Essential Medicines and Health Products, Team of Innovation, Access and Use. The report is an update and extension of the pre-review on cannabidiol, that was prepared by Prof Jason White, Adelaide, Australia, for the 39th ECDD meeting in November 2017. The WHO Secretariat would like to thank the following people for their contribution in producing this review report: Dr Sharon Walsh and Dr Susanna Babalonis, Kentucky USA (update and extension search, review and drafting), and J. Rehm et al, Toronto, Canada (analysis on WHO questionnaire for the Review of Psychoactive Substances for the 40th ECDD: evaluation of Cannabidiol, and report drafting).

Summary

Cannabidiol (CBD) is one of the naturally occurring cannabinoids found in cannabis plants. It is a 21-carbon terpenophenolic compound which is formed following decarboxylation from a cannabidiolic acid precursor, although it can also be produced synthetically.

In experimental models of abuse liability, CBD appears to have little effect on conditioned place preference or intracranial self-stimulation. In an animal drug discrimination model CBD failed to substitute for THC. In humans, CBD exhibits no effects indicative of any abuse or dependence potential.

CBD has been demonstrated as an effective treatment of epilepsy in several clinical trials, with one pure CBD product (Epidiolex®) with completed Phase III trials and under current review for approval in the U.S. There is also preliminary evidence that CBD may be a useful treatment for a number of other medical conditions.

There is unsanctioned medical use of CBD based products with oils, supplements, gums, and high concentration extracts available online for the treatment of many ailments.

CBD is generally well tolerated with a good safety profile. Reported adverse effects may be as a result of drug-drug interactions between CBD and patients' existing medications.

Several countries have modified their national controls to accommodate CBD as a medicinal product.

To date, there is no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD.

1. Substance identification

A. International Nonproprietary Name (INN)

Cannabidiol

B. Chemical Abstract Service (CAS) Registry Number

13956-29-1 [1]

C. Other Chemical Names

CBD;
2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol; [2]

D. Trade Names

Epidiolex® (in development)
Arvisol® (in development)

E. Street Names

No data available

F. Physical Appearance

A crystalline solid [2]

G. WHO Review History

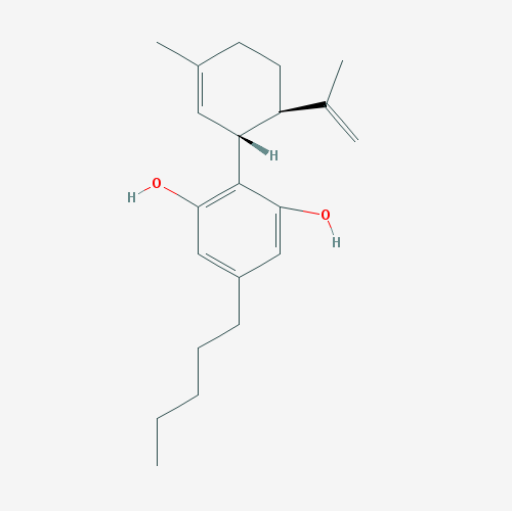
The 38th ECDD recommended that pre-review documentation on cannabis-related substances, including cannabidiol, be prepared and evaluated at a subsequent committee meeting [3]. Cannabidiol has been pre-reviewed by the 39th WHO Expert Committee on Drug Dependence (ECDD) in November 2017. This review is an expansion and update of that initial pre-review report.

2. Chemistry

A. Chemical Name

IUPAC Name: 2-[(6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol

B. Chemical Structure



Molecular Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.469 g/mol

C. Stereoisomers

Cannabidiol (CBD) is normally taken to refer to the naturally occurring (-)-enantiomer. (+) CBD has been synthesized [4] but has received little attention.

(+) CBD has been shown to have modest affinity at CB1 and CB2 receptors unlike (-) CBD ((+)-CBD K_i= 0.84 µM at CB_1), whereas both compounds inhibited anandamide hydrolysis and were agonists at the vanilloid type 1 (VR1) receptor at which capsaicin acts. [5] The (+)-CBD isomer was more active than the (-)-CBD-isomer as an anticonvulsant agent in a mouse seizure model. [6] However, to date, there is no substantive evidence as to whether (+)-CBD is likely to cause THC-like psychoactive effects.

D. Methods and Ease of Illicit Manufacturing

Synthesis of CBD *in vitro*:
Synthetic routes are available for the production of CBD, but some of the published methods yield only small amounts of CBD. The two most efficient routes are:

1) The condensation of (+)-e-mentha-diene-l-01 with olivetol in the presence of weak acids (oxalic, picric or maleic acid). The isomer obtained in this reaction may be converted to CBD with BF_3-etherate by a retro-Friedel-Crafts reaction, followed by recombination. However, with this reagent the reaction proceeds further causing cyclisation of CBD to delta-1-THC and iso-THC [7]

2) A one step reaction for CBD synthesis utilizes boron trifluoride (BF3)-etherate on alumina as condensing reagent in the reaction of (+)-e-mentha-diene-l-01 with olivetol on a 0.8mmol scale (refer to Figure 1). This results in CBD as the major product, with 55% yield as chromatographically pure

oil or 41% yield as crystalline material. On a 100mmol scale, the yields were 46% as an oil, and 37% as crystalline material. [8]

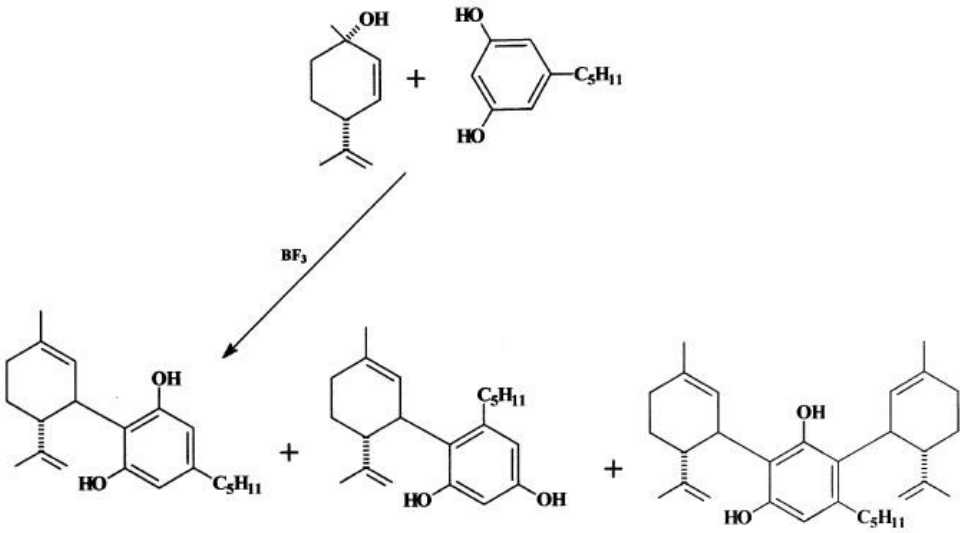


Figure 1: Synthesis of CBD with boron trifluoride (BF3)-etherate taken from Mechoulam et al 2002 [9]

Synthesis of CBD in plants:

Cannabis cultivars range from those grown to produce cannabis for recreational purposes to those produced in order to use hemp fibre derived from the stems of the plant. In cultivars utilized for recreational purposes, the quantity of THC exceeds that of CBD in the dried female inflorescences used for smoking and oral administration. Hemp cultivars produce substantially less THC and higher levels of CBD. [10] Unsanctioned production of cannabis cultivars with high CBD levels does occur for purposes of medical treatment rather than recreational use (refer to Section 13).

In plants, THC and CBD are derived from their acidic precursors Δ^9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) (refer to Figure 2). THCA and CBDA are both derived from cannabigerolic acid (CBGA). The final step differs, with THCA synthase and CBDA synthase producing THCA or CBDA, respectively, from CBGA. Subsequent decarboxylation of THCA and CBDA via light exposure, heating, or aging, results in THC or CBD. [10-12]

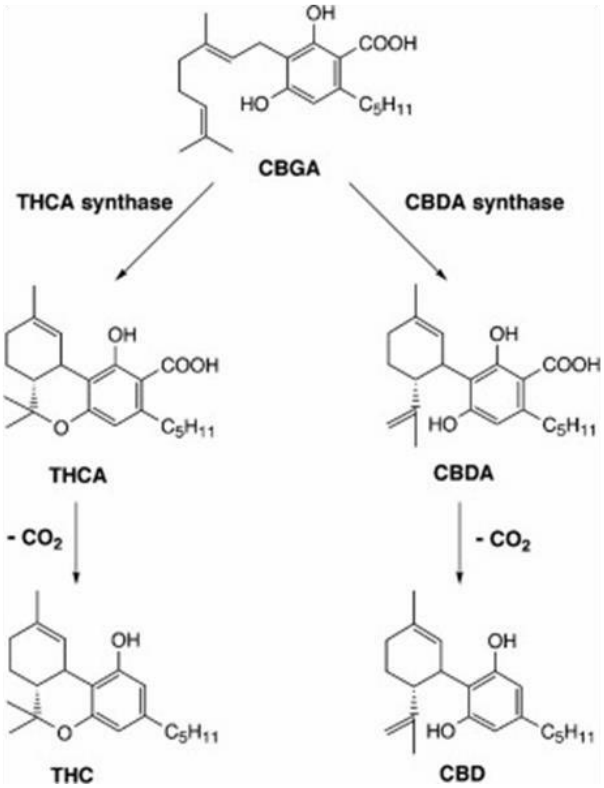


Figure 2: Biogenesis of THC and CBD adapted from Taura et al. (2007) THCA synthase and CBDA synthase catalyze oxidative cyclization of the monoterpene moiety of CBGA to form THCA and CBDA, respectively. THC and CBD are generated from THCA and CBDA by non-enzymatic decarboxylation. [11]

In addition to genetic characteristics, cultivated plants are influenced by environmental conditions and production technology during their life cycle. A study evaluating the effects of ambient temperature and humidity, soil temperature and precipitation on the content of THC and CBD in industrial hemp noted that these agroclimatic conditions have differing effects on THC and CBD. For example, CBD content is positively affected by soil temperature and ambient temperature, but negatively influenced by precipitation [13]

E. Chemical Properties

Melting point: 62-63°C
Solubility: approx. 23.6 mg/mL in DSMO and ethanol [14]

F. Identification and Analysis

There are a number of published methods for the analytical detection of CBD in various biological samples. For example,

- spectrophotometric determination [15];
- liquid chromatography–tandem mass spectrometry (LC–MS/MS) detection of CBD in whole blood [16, 17] samples;

- high performance (HP) LC-MS/MS methods for CBD detection in hair [18], urine [19] and plasma [20] samples;
- gas chromatography mass spectrometry (GC-MS) detection of CBD in hair [21, 22], oral [23] and plasma [24] samples;
- 2-dimensional-GC-MS methods for detection in oral fluid [25], plasma [26] and post mortem blood samples [27].

3. Ease of Convertibility into Controlled Substances

There is some evidence that CBD can be converted to tetrahydrocannabinol (THC), a Schedule 1 substance under the United Nations Convention on Psychotropic Substances 1971. Two main methods have been reported. There have also been reports suggesting this transformation can occur spontaneously *in vivo*; however, additional research has indicated that this finding may be limited to specific experimental conditions and likely does not occur when oral CBD is administered to humans.

Conversion in the laboratory

Under experimental conditions, it has been demonstrated that heating CBD in solutions of some acids catalyses cyclizations within the CBD molecule resulting in delta-9-THC [28]. Gaoni and Mechoulam have published several papers regarding methods of converting CBD to other cannabinoids including THC, however the yields vary, and purity is unclear. [9]

A patent (US 2004/0143126 A1) on the conversion of CBD to delta-9-THC details a method involving the addition of BF_3Et_2O (50 µl), under nitrogen atmosphere, to an ice cold solution of CBD (300 mg) in dry methylene chloride (15 ml). The solution is stirred at 0° C for 1 hour, followed by the addition of saturated aqueous solution of NaHCO3 (2 ml) until the red colour fades. The organic layer is removed, washed with water, dried over $MgSO_4$ and evaporated. The composition of the oil obtained (determined by HPLC) is: trans-delta8-isoTHC 27%, delta-9-THC 66.7%. The oil is then chromatographed on silica gel column (20 g) and eluted with petroleum ether followed by graded mixtures, up to 2:98 of ether in petroleum ether. The first fraction eluted was the delta8-isoTHC (30 mg, 9.5%) followed by a mixture of delta8-iso THC and delta-9-THC (100 mg). The last compound to be eluted was the delta-9-THC (172 mg, 57%). The purity of delta-9-THC (as determined by HPLC) is 98.7%. [29]

Spontaneous conversion

There is some limited evidence that the conversion of CBD to delta-9-THC in the presence of acid could occur in the human gut. Two *in vitro* studies have used simulated gastric fluid to demonstrate the potential for this conversion. One *in vitro* study reported the formation of delta-9-THC along with other cannabinoid products in artificial gastric juice without pepsin. The conversion rate of CBD to THC was only 2.9%. [30]. A more recent publication reported the formation of delta-9-THC and delta-8-THC when CBD was exposed to simulated gastric fluid without enzymes at 37ºC. [31] This study was supported by Zynerba Pharmaceuticals, a company that is developing a transdermal CBD gel (which bypasses gastric involvement and possible conversion). Moreover, a follow-up commentary to this report [32] was also

published (also supported by Zynerba), which suggested that this conversion occurs in humans after oral administration and also suggested that earlier observations from in vivo data of barely detectable concentrations of THC after CBD administration would produce physiological relevant effects in humans.

There is little to no evidence that this conversion occurs *in vivo* after oral administration of CBD. A recent study examined gastric and plasma concentrations of cannabinoids in minipigs after repeated CBD administration (15 mg/kg/day for 5 days). The results indicated no THC or THC metabolites in plasma or gastric fluid matrices after CBD administration. [33] However, this study was supported by GW Pharmaceuticals, a company with an oral CBD product under development.

Overall, there is no evidence that this transformation occurs in humans after oral CBD administration. One human study administered 600 mg of CBD to healthy participants and detected no THC and trace concentrations of THC metabolites (11-OH-THC, THC-COOH). [34] Similarly, chronic administration of CBD does not result in detectable THC concentrations in plasma; for example, in a six-week clinical study in Huntington's disease patients who were administered CBD 10 mg/kg/day (approximately 700 mg/day), CBD average plasma concentration range was 5.9-11.2 ng/mL with no delta-9-THC detected. [35].

In general, clinical studies have reported that even high doses of oral CBD do not cause THC-like effects (e.g., impairment, increased heart rate/tachycardia, dry mouth).[36] For example, in a study of healthy volunteers administered 200 mg oral CBD, CBD did not produce any impairments of motor or psychomotor performance.[37] A number of other studies involving high doses of CBD were recently summarised by Grotenhermen et al.[36] and Nahler et al.[38]; they concluded that high doses of oral CBD consistently fail to demonstrate significant effects or demonstrate effects opposite to those of THC. Overall, there is no evidence of that oral CBD administration in humans results in clinically relevant THC-like subjective or physiological effects, or appreciable plasma concentrations of THC or its metabolites.

4. General Pharmacology

A. Routes of administration and dosage

Currently there are no approved marketed pure CBD medicinal products, although several are in development (refer to Section 11).

In clinical trials and research studies, CBD is generally administered orally as either a capsule, or dissolved in an oil solution (e.g. olive or sesame oil). It can also be administered through sublingual or intranasal routes. A wide range of oral doses have been reported in the literature, with most from 100-800mg/day. [39]

B. Pharmacokinetics

Oral delivery of an oil-based capsule formulation of CBD has been assessed in humans. Probably due to its poor aqueous solubility, the absorption of CBD from the gastrointestinal tract is erratic, and the resulting pharmacokinetic profile is variable. Bioavailability from oral delivery was estimated to be 6% due to significant first-pass metabolism. [40] In healthy male volunteers, the

mean±SD whole blood levels of CBD at 1, 2 and 3 hours after administration of 600mg oral CBD were reported to be 0.36 (0.64) ng/mL, 1.62 (2.98) ng/mL and 3.4 (6.42) ng/mL, respectively. [34] A recent study reported that CBD, when given at doses of 5, 10 and 20 mg/kg/d to children ages 4-10 with Dravet syndrome, produced dose-proportional increases in area-under-the-curve plasma concentrations for CBD and its metabolites, 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD. [41] Aerosolised CBD has been reported to yield rapid peak plasma concentrations in 5–10 minutes and higher bioavailability than oral administration.

CBD is rapidly distributed into the tissues with a high volume of distribution of ~32L/kg. Like THC, CBD may preferentially accumulate in adipose tissues due to its high lipophilicity. [39, 42]

CBD is extensively metabolised in the liver. The primary route is hydroxylation to 7-OH-CBD which is then metabolised further resulting in a number of metabolites that are excreted in faeces and urine. [40] A study in human liver microsomes (HLMs) demonstrated that CBD was metabolized by pooled HLMs to eight monohydroxylated metabolites (6α-OH-, 6β-OH-,7-OH-, 1”-OH-, 2”-OH-, 3”-OH-, 4”-OH-, and 5”-OH-CBDs). Among these metabolites, 6α-OH-, 6β-OH-, 7-OH-, and 4”-OH-CBDs were the major ones. Seven recombinant human CYP enzymes were identified as capable of metabolising CBD: CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5. The two main isoforms involved are CYP3A4 and CYP2C19. [43]

In a number of studies, CBD has been shown to inhibit CYP isozymes *in vitro*, but it is not clear that this occurs at concentrations achieved with doses used clinically.

C. Pharmacodynamics

There are two main cannabinoid (CB) receptors, CB_1 which is primarily located in the central nervous system with some expression in peripheral tissues and CB_2 receptors, which can be found in the periphery on cells with immune function and in the gastrointestinal tract and at low densities in the central nervous system.

CBD does not appear to act directly at CB_1 receptors, with a number of studies reporting that there is no measurable response in binding assays. In studies examining potential agonist effects at CB_1 receptors, most find no effect, with one report of a weak agonist and one of a weak antagonist effect, each at high concentrations (>10uM). CBD also shows low affinity at CB_2 receptors. [44]

Across a range of measures in humans and animals, CBD had been shown to have very different effects from those of THC. In mice, CBD failed to produce the behavioral characteristics (e.g. suppression of locomotor activity, hypothermia, antinociception) associated with CB_1 activation, whereas THC generated all of the effects which occur when CB_1 is activated. [45, 46] Neuroimaging studies in humans and animals have shown that CBD has effects which are generally opposite to those of THC. [47] In contrast to THC, CBD has no effect on heart rate or blood pressure under normal conditions, but in animal models of stress it reduces heart rate and blood pressure. [48] Other differences between THC and CBD are discussed below.

Some studies have shown that CBD may reduce or antagonize some of the effects of THC. The mechanism for this is unclear, with some suggesting that it may be a weak CB_1 antagonist. Recent evidence suggests that it may be a negative allosteric modulator of the CB_1 receptor, thereby acting as a non-competitive antagonist of the actions of THC and other CB_1 agonists. [44, 49] A recent study suggests that CBD may also act as an allosteric modulator at the CB_2 receptor. [50]

CBD may also interact with the endocannabinoid system through indirect mechanisms such as enhanced action of the endogenous cannabinoid ligand anandamide. This results from blockade of anandamide reuptake and the inhibition of its enzymatic degradation. [5, 9, 43]

CBD has been shown to modulate several non-endocannabinoid signaling systems. It is not clear which, if any, of these mechanisms are responsible for any of CBD's potential clinical or other effects. Some of these mechanisms include [51]:

- Inhibition of adenosine uptake, possibly resulting in indirect agonist activity at adenosine receptors.
- Enhanced activity at the $5\text{-}HT_{1a}$ receptor.
- Enhanced activity at glycine receptor subtypes
- Blockade of the orphan G-protein-coupled receptor GPR55

5. Toxicology

The potential toxic effects of CBD have been extensively reviewed [52] with a recent update of the literature. [53] In general, CBD has been found to have relatively low toxicity, although not all potential effects have been explored. The following are some of the relevant findings to date from *in vitro* and animal studies:

- CBD affects growth of tumoral cell lines, but has no effect in most non-tumour cells. However, a pro-apoptotic effect has been observed in lymphocytes.
- It has no effect on embryonic development (limited research)
- Evidence on potential hormonal changes is mixed, with some evidence of possible effects and other studies suggesting no effect, depending on the method used and the particular hormone
- It has no effect on a wide range of physiological and biochemical parameters or significant effects on animal behaviour unless extremely high doses are administered (e.g., in excess of 150 mg/kg iv as an acute dose or in excess of 30 mg/kg orally daily for 90 days in monkeys)
- Effects on the immune system are unclear; there is evidence of immune suppression at higher concentrations, but immune stimulation may occur at lower concentrations.
- There is potential for CBD to be associated with drug interactions through inhibition of some cytochrome P450 enzymes, but it is not yet clear whether these effects occur at physiological concentrations.

6. Adverse Reactions in Humans

As noted above, CBD does not produce the effects that are typically seen with cannabinoids such as THC. It also failed to produce significant effects in a human

study of abuse potential discussed below. [34] Across a number of controlled and open label trials CBD of the potential therapeutic effects of CBD it is generally well

tolerated, with a good safety profile. [39, 53] Clinical trials involving use of CBD for treatment of epilepsy will be discussed in Section 9: Therapeutic Applications.

7. Dependence Potential

A. Animal Studies

Male mice were injected i.p. once a day for 14 days with either CBD (0.1, 1, or 3mg/kg) or delta-9-THC (1, 3, or 10mg/kg). Tolerance to the effects of THC was observed, however no tolerance to CBD at any of the dosages was observed. [54] No studies of the physical dependence potential of CBD in animals were identified.

B. Human Studies

Controlled, human studies regarding the potential physical dependence effects (e.g. withdrawal and tolerance) of cannabidiol have not been reported.

8. Abuse Potential

A. Animal Studies

In male Sprague-Dawley rats, administration of low dose (5 mg/kg) CBD did not change the threshold frequency required for intracranial self-stimulation (ICSS). However, high dose (10 mg/kg and 20 mg/kg) CBD resulted in an elevation of the threshold suggestive of diminished reward activity. This effect is opposite to that of drugs of abuse such as cocaine, methamphetamine and opioids which lower the threshold. [55]

Increased dopamine release in cells of the mesolimbic ventral tegmental area – nucleus accumbens pathway is a common effect characteristic of almost all drugs of abuse. While THC has been shown to increase the firing rate of these cells, cannabidiol had no effect. [56]

It appears that CBD given alone has little effect on conditioned place preference (CPP). For example, Long-Evans rats treated with 10 mg/kg CBD showed neither CPP nor CPA. [57] However, rats treated with increasing doses of CBD and THC (1, 3, and 10 mg/kg) exhibited a trend towards CPP not seen in those given THC alone. [58] The authors attributed this to a pharmacokinetic interaction leading to higher THC concentrations rather than a change in receptor action.

CBD appears not to exhibit THC-like discriminative stimulus effects. For example, in rats trained to discriminate THC from vehicle, CBD did not substitute for THC at any dose tested [57]. CBD also failed to substitute for THC in pigeons trained to discriminate THC from vehicle. [59]

B. Human Studies

While the number of studies is limited, the evidence from well controlled human experimental research indicates that CBD is not associated with abuse potential.

Single dose administration of cannabidiol has been evaluated in healthy volunteers using a variety of tests of abuse potential as well as physiological effects in a randomised double blind placebo-controlled trial. [34] An orally administered dose of 600mg of CBD did not differ from placebo on the scales of the Addiction Research Centre Inventory, a 16 item Visual Analogue Mood Scale, subjective level of intoxication or psychotic symptoms. In contrast, THC (10mg oral) administration was associated with subjective intoxication and euphoria as well as changes in ARCI scales reflecting sedation and hallucinogenic activity. THC also increased psychotic symptoms and anxiety. While THC increased heart rate, CBD had no physiological effects.

A randomized, double-blind, within-subject laboratory study was undertaken to assess the influence of CBD (0, 200, 400, 800mg, p.o.) pre-treatment on the effects of inactive (0.01% THC) and active (5.30–5.80% THC) smoked cannabis. Healthy cannabis smokers (n=31) completed eight outpatient sessions with CBD administered 90min prior to cannabis administration. Under placebo CBD conditions, active cannabis was self-administered by significantly more participants and produced significant, time-dependent increases in subjective ratings and heart rate relative to inactive cannabis. CBD alone produced no significant psychoactive, cardiovascular or other effects. Cannabis self-administration, subjective effects, and cannabis ratings did not vary as a function of CBD dose relative to placebo capsules. These findings suggest that oral CBD does not reduce the reinforcing, physiological, or positive subjective effects of smoked cannabis. [60]

The authors of the study then undertook a second analysis of this data to examine the abuse liability profile of oral cannabidiol in comparison to oral placebo and active smoked cannabis. The results of this analysis demonstrated that CBD was placebo-like on all measures (including visual analogue scales, psychomotor performance such as the digit symbol substitution task, heart rate and blood pressure) compared to active cannabis, which produced abuse-related subjective effects as well as a range of other effects. [61]

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Epilepsy

The clinical use of CBD is most advanced in the treatment of epilepsy. In clinical trials, CBD has been demonstrated as an effective treatment for at least some forms of epilepsy, with one pure CBD product (Epidiolex®) currently in Phase III trials.

The use of CBD for this purpose is based on a number of studies in animals dating back to the 1970s. [62] These studies demonstrated the anti-seizure activity of cannabidiol in a number of animal models. Based on this research, cannabidiol has been tested in patients with epilepsy.

In a very early small-scale double-blind placebo-controlled trial, patients received either 200 mg CBD daily (4 patients) or placebo (5 patients) for a 3-month period, in addition to their habitual medication. In the CBD group, two patients had no seizures for the entire 3-month period, one partially improved, and the fourth had no

improvement. No improvements were observed in the placebo group and no toxic effects were reported for either group. This study has a number of limitations, including the small sample size, unclear design as to blinding, and lack of definition of partial improvement. [63]

In another study, 15 patients with "secondarily generalized epilepsy with temporal focus," were randomly divided into two groups. In a double-blind procedure, each patient received 200-300 mg daily of CBD or placebo for up to four and a half months in combination with their existing prescribed antiepileptic medications (which were no longer effective in the control of their symptoms). CBD was tolerated in all patients, with no signs of toxicity or serious side effects. Of the eight participants in the CBD treatment group, four were reported to be almost free of seizure episodes throughout the trial, whereas three others showed partial clinical improvement. CBD was ineffective in one patient. In comparison, the clinical condition of seven placebo patients remained unchanged with one patient showing improvement. [64]

There have also been some negative reports regarding the effectiveness of CBD. In a trial reported in 1986, a dose of CBD of 200–300 mg/day for a month resulted in no significant differences between the treatment and placebo groups. [65] Similarly, a 6-month double blind study administering CBD 100 mg 3 times each day did not result in any changes in seizure frequency or improvement in cognition or behaviour. [66]

The results of several trials examining the effects of CBD in patients with severe, intractable, childhood-onset, treatment-resistant epilepsy have been reported. The first was an open label study of 214 patients (aged 1–30 years) who were receiving stable doses of antiepileptic drugs before study entry. Patients were given oral cannabidiol, initially at 2–5 mg/kg per day, and then titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day, dependent on study site. The primary measure was the percentage change in the frequency of seizures. In the CBD group, the median monthly frequency of motor seizures reduced from 30·0 at baseline to 15·8 over the 12-week treatment period. The trial was also designed to assess safety, but the absence of a control group means that the results cannot be used to assess the likelihood of CBD producing particular effects. Adverse events reported in more than 10% of patients were somnolence, decreased appetite, diarrhoea, fatigue, and convulsion. Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, of which 20 (12%) experienced severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). [67]

The same research group reported the results of a controlled trial of CBD treatment for Dravet syndrome, a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. In a double-blind, placebo-controlled trial, 120 children and young adults with Dravet syndrome were randomly assigned to receive either cannabidiol oral solution (20 mg per kilogram per day) or placebo, in addition to standard antiepileptic treatment (a median of 3.0 drugs). The authors reported that cannabidiol decreased the median frequency of convulsive seizures per month from 12.4 to 5.9, as compared with a decrease from 14.9 to 14.1 with placebo. A small percentage (5%) of patients in the CBD group became seizure free as compared to zero in the placebo group. Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhoea (31% vs 10%), loss of appetite (28% vs 5%) and somnolence (36% vs 10%). Other adverse effects noticed were vomiting, fatigue, pyrexia and abnormal results on liver-function tests.

Adverse effects led to the withdrawal of eight patients in the cannabidiol group compared with one in the placebo group. [68]

A similar study was recently conducted and reported on the safety and efficacy of CBD in patients with Lennox-Gastaut syndrome, a severe form of epileptic encephalopathy that produces various types of seizures (including drop seizures) that are often treatment-resistant. Across 24 clinical sites (located in US, the Netherlands and Poland), a total of 171 patients ages 2-55 years old, were randomized to receive active CBD [200 mg/kg, oral solution] (n=86) or matched placebo (n=85) as an add-on to their antiepileptic regimen (average of 3 medications/patient in each group). CBD was administered daily for 14 weeks: 2 weeks of dose escalation (starting dose of 2.5 mg/kg, PO) and 12 weeks of maintenance (200 mg/kg, PO); a 10-day dose taper was also included at the end of treatment. The authors report that CBD treatment decreased drop seizure frequency by a median of 43.9% (71.4 seizures per patient/month at baseline; 31.4 during treatment), compared to a 21.8% reduction in the placebo group (74.7 at baseline, 56.3 during treatment). CBD also increased the number of patients experiencing ≥50% reduction in drop seizure frequency (44% patients (n=38) in the CBD group compared to 24% (n=20) in the placebo group). CBD also reduced other non-drop seizures (49.4% reduction in CBD group, 22.9% in the placebo group). A small number of patients in the CBD group (n=3) were seizure free during the 12 weeks of maintenance dosing, compared to zero in the placebo group. Treatment related adverse events occurred more frequently in the cannabidiol group than in the placebo group and were similar to those reported in previous trials: diarrhoea (13% vs 4%), somnolence (14% vs. 8%), decreased appetite (9% vs 1%), vomiting (7% vs. 5%) and pyrexia (1% in both groups). Increases in liver function tests (>3 times the upper limit of normal) occurred in 20 patients in the CBD group and 1 patient in the placebo group. [69]

It has been suggested that some of the adverse effects of cannabidiol observed in the clinical studies may relate to interactions with other antiepileptic drugs. For example, a recent study evaluated thirteen subjects with refractory epilepsy concomitantly taking clobazam and CBD. Nine of 13 subjects had a >50% decrease in seizures, corresponding to a responder rate of 70%. Side effects were reported in 10 (77%) of the 13 subjects, but were alleviated with clobazam dose reduction. All subjects tolerated CBD well. [70]

Cannabidiol (as Epidiolex®; GW Pharmaceuticals) was submitted in 2017 for regulatory approval to the U.S. Food and Drug Administration for treatment of seizures related to Lennox-Gastaut and Dravet syndromes in patients two years of age and older. A public advisory committee was held in April 2018 with the committee voting in favor of approval of CBD; while the committee approval is not binding but rather advisory, it is most common for the FDA to concur with committee votes.

Other indications

There is also evidence that CBD may be a useful treatment for a number of other medical conditions. However, this research is considerably less advanced than for treatment of epilepsy. For most indications, there is only pre-clinical evidence, while for some there is a combination of pre-clinical and limited clinical evidence. The range of conditions for which CBD has been assessed is diverse, consistent with its neuroprotective, antiepileptic, hypoxia-ischemia, anxiolytic, antipsychotic, analgesic, anti-inflammatory, anti-asthmatic, and antitumor properties. [39, 53, 71] The evidence for some of these indications was recently reviewed by Pisanti et al.,.[72]

Additionally, recent human studies have reported a therapeutic signal for CBD for transplant acceptance (decreasing the development of graft vs. host disease after hematopoietic cell transplants) [73] and reducing some of the positive symptoms of schizophrenia (1000 mg/day, PO) [74]. Other recent reports have failed to demonstrate CBD efficacy to reduce symptoms of ulcerative colitis (up to 500 mg/day, PO) [75], chronic pain in kidney transplant patients (50 – 300 mg/day, PO) [76], and experimentally-induced anxiety (600 mg, PO). [77]

Another possible therapeutic application which has been investigated is the use of CBD to treat drug addiction. A recent systematic review concluded that there were a limited number of preclinical studies which suggest that CBD may have therapeutic properties on opioid, cocaine, and psychostimulant addiction, and some preliminary data suggest that it may be beneficial in cannabis and tobacco addiction in humans. However, considerably more research is required to evaluate CBD as a potential treatment. [78]

10. Listing on the WHO Model List of Essential Medicines

Cannabidiol is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List). [79]

11. Marketing Authorizations (as a Medicinal Product)

There are currently no authorized pure CBD products. However, there are several in development.

Epidiolex® is a liquid oral formulation of pure plant-derived CBD. It is produced by GW Pharmaceuticals in the United Kingdom and has shown positive results in Phase 3 trials for Dravet and Lennox-Gastaut syndromes, which are both treatment-resistant seizure disorders. The published results related to this therapeutic application are covered in Section 9: Therapeutic Applications. [67-70]

Arvisol® is an oral tablet containing pure CBD. It has been developed by Echo Pharmaceuticals in the Netherlands and is intended to be registered for the treatment of various neurological disorders, including schizophrenia and epilepsy. Arvisol® is still undergoing Phase I clinical trials and is not yet available as a medicinal product. [80]

Zynerba® Pharmaceuticals is developing a CBD gel (ZYN002) that is designed for transdermal use. The target indications for ZYN002 are Fragile X syndrome, adult refractory focal epilepsy and encephalopathies that are developmental and epileptic in nature. This formulation is currently in open-label Phase 2 testing for Fragile X syndrome. Dosing recommendations are to begin at 50 mg/day with increases up to 250 mg/day. [81]

Bionorica® (Germany) has developed a pure CBD product that is extracted from hemp plants through a multi-stage process into a crystalline powder (production completed by THC Pharm). [82]

STI Pharmaceuticals (Essex, United Kingdom) has developed a crystalline powder of pure synthetic CBD with multiple doses. This product has been evaluated in a Phase II study for its effects on marijuana-induced subjective effects in an oral capsule formulation (200-800 mg). [60] Additionally, STI has produced an aerosolized

formulation for inhalation that was assessed using an ad lib dosing design (400 ug/spray) for cigarette smoking . [83] Finally, another study examined CBD dissolved in olive oil as an oral preparation for graft versus host disease. [73]

INSYS Pharmaceuticals (United States) has developed an oral solution of pure CBD. It is currently in Phase 2 trials for childhood absence seizures (20-40 mg) and in a Phase 3 trial as an adjunctive therapy in conjunction with vigabatrin for infantile spasm-type seizures. Phase 2 trials are currently registered for Prader-Willi syndrome, and there is open-label access testing for treatment-resistant seizure disorders. This product has also been in a human laboratory trial and evaluated for anxiety-like behavior at doses from 300-900 mg with negative findings .[84]

PhytoTech Therapeutics (Tel Aviv, Israel) is developing an oral formulation (PTL101) that contains purified CBD embedded in gelatin matrix pellets. Phase 1 testing has been conducted on this product (10 to 100 mg) and found that it had significantly greater bioavailability compared to a reference product containing CBD (see Sativex® below). [85]

Ananda Scientific (Israel) is producing pure CBD for medicinal purposes and reports having their Phase 1 pharmacokinetics studies underway presently in Israel, with numerous other trials planned in Israel and China. [86]

In 2015, the US Food and Drug Administration (FDA) granted GW Pharmaceuticals Fast Track designation for intravenous CBD to treat Neonatal Hypoxic-Ischemic Encephalopathy (NHIE).[87] The European Commission also granted orphan designation (EU/3/15/1520) for cannabidiol to be used in the treatment of perinatal asphyxia.[88] NHIE and Perinatal Asphyxia are forms of acute or sub-acute brain injury due to asphyxia caused during the birth process and resulting from deprivation of oxygen during birth (hypoxia). Currently there are no other treatments available for these conditions, but there is evidence of the effectiveness of cannabidiol in animal models. [89]

There are numerous CBD products including purported medicinal products, such as pills and capsules for various diseases/symptoms, and also lotions, oils, foods, drinks, shampoos, cosmetics, etc. that are being manufactured and distributed without regulatory oversight and often with unverified contents. [90] The U.S. Food and Drug Administration has issued two major series of warning letters to manufacturers for fraudulent medical claims (describing health benefits with no evidence) and fraudulent production claims (marketing products as containing specified concentrations of CBD when testing demonstrates the absence of CBD). [91]

CBD Combination Products

CBD is presently marketed in combination with THC in a 1:1 ratio (Sativex®), which is marketed by GW Pharmaceuticals in a number of countries. [92] This combination is sometimes referred to as nabiximols, a name given by the United States Adopted Names (USAN) Council. This product will be covered in a separate ECDD review.

12. Industrial Use

Pure CBD has no legitimate industrial uses.

13. Non-Medical Use, Abuse and Dependence

At present, there are no case reports of abuse or dependence relating to the use of pure CBD. There are also no published statistics on non-medical use of pure CBD.

There is unsanctioned medical use of CBD based products. These are produced from high CBD content plants and distributed in a variety of forms, including oils and capsules. These products are sold online as unapproved treatments for a variety of disorders including epilepsy, cancer, AIDS/HIV, anxiety, arthritis, pain, and post-traumatic stress disorder (PTSD). Additionally, CBD is being used in skin and beauty products such as shampoos and skin creams. [93, 94] Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

At present no public health problems (e.g. driving under the influence of drugs cases, comorbidities) have been associated with the use of pure CBD.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances for the 40th ECDD: evaluation of Cannabidiol.

15. Licit Production, Consumption and International Trade

Licit production of CBD for medical purposes is described in Section 11.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances for the 40th ECDD: evaluation of Cannabidiol.

16. Illicit Manufacture and Traffic and Related Information

There are no published statistics (e.g. country data on seizures of illicit CBD) currently available.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances for the 40th ECDD: evaluation of Cannabidiol.

17. Current International Controls and Their Impact

Cannabidiol is not listed in the schedules of the 1961, 1971 or 1988 United Nations International Drug Control Conventions. [95]

However, cannabidiol is being produced for pharmaceutical purposes as an extract of cannabis by GW Pharmaceuticals. Cannabidiol that is produced as an extract of cannabis is currently included in Schedule I of the 1961 Convention.

18. Current and Past National Controls

United Kingdom: A statement was issued by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2016 that products containing CBD used for medical purposes are considered as a medicine subject to standard licensing requirements. [96]

United States: CBD is one of many cannabinoids present in cannabis, and as such is in Schedule I of the Controlled Substances Act (Schedule I is the most restricted/ regulated drug class, reserved for medications with a high potential for abuse and no currently accepted medical use).

Canada: CBD is specifically listed in 'Cannabis, its preparations and derivatives' as a controlled substance listed in Schedule II Controlled Drugs and Substances Act. However, in 2016 Canada's Access to Cannabis for Medical Purposes Regulations came into effect. These regulations improve access to cannabis used for medicinal purposes, including CBD. [97]

Australia: In 2015, CBD in preparations for therapeutic use containing 2 per cent or less of other cannabinoids found in cannabis was placed in Schedule 4 as a 'Prescription Only Medicine OR Prescription Animal Remedy'. Previous to this it was captured in Schedule 9 as a prohibited substance. [98]

New Zealand: CBD is a controlled drug. However, by passing the Misuse of Drugs Amendment Regulations 2017 in September 2017, many of the restrictions currently imposed by the regulations are removed since then. The changes will mean that CBD products, where the level of other naturally occurring cannabinoids is less than 2% of the cannabinoid content, will be easier to access for medical use. [99]

Switzerland: CBD is not subject to the Narcotics Act because it does not produce a psychoactive effect. It is still subject to standard Swiss legislation. [100]

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None

References

1. NCBI. PubChem Compound Database; CID=26346 August 1 2017]; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/26346
2. Cayman Chemical. *Cannabidiol (DEA Schedule I Regulated Compound)*. Safety Data Sheet 2015; Available from: https://www.caymanchem.com/msdss/90080m.pdf.
3. *WHO Expert Committee on Drug Dependence : thirty-eighth report. Geneva: World Health Organization; 2017 (WHO technical report series ; no. 1005). Licence: CC BY-NC-SA 3.0 IGO.*
4. Shah, V.J., *Synthesis of cannabidiol stereoisomers and analogs as potential anticonvulsant agents*. The University of Arizona.
5. Bisogno, T., et al., *Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide*. British Journal of Pharmacology, 2001. **134**(4): p. 845-852.
6. Leite, J., et al., *Anticonvulsant Effects of the (–) and (+)Isomers of Cannabidiol and Their Dimethylheptyl Homologs*. Vol. 24. 1982. 141-6.
7. Petrzilka, T., W. Haefliger, and C. Sikemeier, *Synthese von Haschisch-Inhaltsstoffen. 4. Mitteilung.* Helvetica Chimica Acta, 1969. **52**(4): p. 1102-1134.
8. Baek, S.-H., M. Srebnik, and R. Mechoulam, *Boron triflouride etherate on alimina - a modified Lewis acid reagent. An improved synthesis of cannabidiol*. Vol. 26. 1985. 1083–1086.
9. Mechoulam, R. and L. Hanus, *Cannabidiol: an overview of some chemical and pharmacological aspects. Part I: chemical aspects.* Chem Phys Lipids, 2002. **121**(1-2): p. 35-43.
10. Marks, M.D., et al., Identification of candidate genes affecting Δ(9)-*tetrahydrocannabinol biosynthesis in Cannabis sativa.* Journal of Experimental Botany, 2009. **60**(13): p. 3715-3726.
11. Taura, F., et al., *Cannabidiolic-acid synthase, the chemotype-determining enzyme in the fiber-type Cannabis sativa.* FEBS Letters, 2007. **581**(16): p. 2929-2934.
12. Russo, E.B., *Cannabidiol Claims and Misconceptions.* Trends in pharmacological sciences, 2017. **38**(3): p. 198-201.
13. Sikora, V., et al., *Influence of agroclimatic conditions on content of main cannabinoids in industrial hemp (Cannabis sativa L.)*. Vol. 43. 2011.
14. Tocris Bioscience. https://www.tocris.com/products/minus-cannabidiol_1570#product-details.
15. Aman, T., A. Rashid, and I. Khokhar, *Spectrophotometric Determination of Cannabidiol.* Analytical Letters, 1993. **26**(10): p. 2113-2125.
16. Schwope, D.M., K.B. Scheidweiler, and M.A. Huestis, *Direct quantification of cannabinoids and cannabinoid glucuronides in whole blood by liquid chromatography–tandem mass spectrometry.* Analytical and Bioanalytical Chemistry, 2011. **401**(4): p. 1273.
17. Sorensen, L.K. and J.B. Hasselstrom, *Sensitive Determination of Cannabinoids in Whole Blood by LC-MS-MS After Rapid Removal of Phospholipids by Filtration.* J Anal Toxicol, 2017. **41**(5): p. 382-391.
18. Salomone, A., et al., *Simultaneous analysis of several synthetic cannabinoids, THC, CBD and CBN, in hair by ultra-high performance liquid chromatography tandem mass spectrometry. Method validation and application to real samples.* J Mass Spectrom, 2012. **47**(5): p. 604-10.
19. Wei, B., L. Wang, and B.C. Blount, *Analysis of Cannabinoids and Their Metabolites in Human Urine.* Anal Chem, 2015. **87**(20): p. 10183-7.
20. Aizpurua-Olaizola, O., et al., *Simultaneous quantification of major cannabinoids and metabolites in human urine and plasma by HPLC-MS/MS and enzyme-alkaline hydrolysis.* Drug Test Anal, 2017. **9**(4): p. 626-633.

21. Cirimele, V., et al., *Testing human hair for Cannabis. III. rapid screening procedure for the simultaneous identification of delta 9-tetrahydrocannabinol, cannabinol, and cannabidiol.* J Anal Toxicol, 1996. **20**(1): p. 13-6.
22. Kim, J.Y., et al., *Simultaneous determination of cannabidiol, cannabinol, and delta9-tetrahydrocannabinol in human hair by gas chromatography-mass spectrometry.* Arch Pharm Res, 2005. **28**(9): p. 1086-91.
23. Moore, C., S. Rana, and C. Coulter, *Simultaneous identification of 2-carboxy-tetrahydrocannabinol, tetrahydrocannabinol, cannabinol and cannabidiol in oral fluid.* J Chromatogr B Analyt Technol Biomed Life Sci, 2007. **852**(1-2): p. 459-64.
24. Andrenyak, D.M., et al., *Determination of -9-Tetrahydrocannabinol (THC), 11-hydroxy-THC, 11-nor-9-carboxy-THC and Cannabidiol in Human Plasma using Gas Chromatography-Tandem Mass Spectrometry.* J Anal Toxicol, 2017. **41**(4): p. 277
25. Milman, G., et al., *Cannabinoids and Metabolites in Expectorated Oral Fluid Following Controlled Smoked Cannabis.* Clinica Chimica Acta; International Journal of Clinical Chemistry, 2012. **413**(7-8): p. 765-770.
26. Karschner, E.L., et al., *Validation of a Two-Dimensional Gas Chromatography Mass Spec*trometry Method for the Simultaneous Quantification of Cannabidiol, Δ(9)-*Tetrahydrocannabinol (THC), 11-Hydroxy-THC and 11-nor-9-Carboxy-THC in Plasma.* Analytical and bioanalytical chemistry, 2010. **397**(2): p. 603-611.
27. Andrews, R. and S. Paterson, *A validated method for the analysis of cannabinoids in post-mortem blood using liquid-liquid extraction and two-dimensional gas chromatography-mass spectrometry.* Forensic Sci Int, 2012. **222**(1-3): p. 111-7.
28. Gaoni, Y. and R. Mechoulam, *Hashish-VII. The isomerization of cannabidiol to tetrahydrocannabinols*. Vol. 22. 1966. 1481–1488.
29. Webster, G.R., L. Sarna, and R. Mechoulam, *Conversion of cbd to delta8-thc and delta9-thc*. 2004, Google Patents.
30. Watanabe, K., et al., Conversion of cannabidiol to Δ9-*tetrahydrocannabinol and related cannabinoids in artificial gastric juice, and their pharmacological effects in mice.* Forensic Toxicology, 2007. **25**(1): p. 16-21.
31. Merrick, J., et al., *Identification of psychoactive degradants of cannabidiol in simulated gastric and physiological fluid.* Cannabis and Cannabinoid Research, 2016. **1**(1): p. 102-112.
32. Bonn-Miller, M.O., S.L. Banks, and T. Sebree, *Conversion of Cannabidiol Following Oral Administration: Authors' Response to Grotenhermen et al. DOI: 10.1089/can. 2016.0036.* Cannabis and Cannabinoid Research, 2017. **2**(1): p. 5-7
33. Wray, L., C. Stott, N. Jones, and S. Wright, *Cannabidiol Does Not Convert to Δ9-Tetrahydrocannabinol in an In Vivo Animal Model.* Cannabis and Cannabinoid Research, 2017. **2**(1): p. 282-287.
34. Martin-Santos, R., et al., *Acute effects of a single, oral dose of d9- tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers.* Curr Pharm Des, 2012. **18**(32): p. 4966-79.
35. Consroe, P., et al., *Controlled clinical trial of cannabidiol in Huntington's disease.* Pharmacology Biochemistry and Behavior, 1991. **40**(3): p. 701-708.
36. Grotenhermen, F., E. Russo, and A.W. Zuardi, *Even High Doses of Oral Cannabidol Do Not Cause THC-Like Effects in Humans: Comment on Merrick et al. Cannabis and Cannabinoid Research 2016;1(1):102–112; DOI: 10.1089/can.2015.0004.* Cannabis and Cannabinoid Research, 2017. **2**(1): p. 1-4.
37. Consroe, P., et al., *Interaction of cannabidiol and alcohol in humans.* Psychopharmacology, 1979. **66**(1): p. 45-50.
38. Nahler, G., et al., *A Conversion of Oral Cannabidiol to Delta9-Tetrahydrocannabinol Seems Not to Occur in Humans. Cannabis and Cannabinoid Research, 2017. **2**(1): p. 81-86*
39. Fasinu, P.S., et al., *Current Status and Prospects for Cannabidiol Preparations as*

New Therapeutic Agents. Pharmacotherapy, 2016. **36**(7): p. 781-96.
40. Hawksworth, G. and K. McArdle, *Metabolism and pharmacokinetics of cannabinoids.* The Medicinal Uses of Cannabis and Cannabinoids. Pharmaceutical Press, London, 2004: p. 205-228.
41. Devinsky, O., et al., *Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome.* Neurology, 2018. **90**(14): p. e1204-e1211.
42. Ohlsson, A., et al., *Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration.* Biological Mass Spectrometry, 1986. **13**(2): p. 77-83.
43. Jiang, R., et al., *Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes.* Life Sci, 2011. **89**(5-6): p. 165-70.
44. McPartland, J.M., et al., *Are cannabidiol and* Δ9*-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review.* British Journal of Pharmacology, 2015. **172**(3): p. 737-753.
45. Pertwee, R., *The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin.* British journal of pharmacology, 2008. **153**(2): p. 199-215.
46. Long, L.E., et al., A behavioural comparison of acute and chronic Δ9-*tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice.* International Journal of Neuropsychopharmacology, 2010. **13**(7): p. 861-876.
47. Batalla, A., et al., *Neuroimaging studies of acute effects of THC and CBD in humans and animals: a systematic review.* Current pharmaceutical design, 2014. **20**(13): p. 2168-2185.
48. Sultan, S.R., et al., *A systematic review and meta-analysis of the haemodynamic effects of Cannabidiol.* Frontiers in pharmacology, 2017. **8**.
49. Laprairie, R., et al., *Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor.* British journal of pharmacology, 2015. **172**(20): p. 4790-4805.
50. Martínez-Pinilla, E. et al., *Binding and signaling studies disclose a potential allosteric site for cannabidiol in cannabinoid CB_2 receptors*. Frontiers in Pharmacology, 2017. **8**(744): p. 1-10.
51. Bih, C.I., et al., *Molecular targets of cannabidiol in neurological disorders.* Neurotherapeutics, 2015. **12**(4): p. 699-730.
52. Machado Bergamaschi, M., et al., *Safety and side effects of cannabidiol, a Cannabis sativa constituent.* Current drug safety, 2011. **6**(4): p. 237-249.
53. Iffland, K. and F. Grotenhermen, *An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies.* Cannabis and Cannabinoid Research, 2017. **2**(1): p. 139-154.
54. Hayakawa, K., et al., Repeated treatment with cannabidiol but not Δ9-*tetrahydrocannabinol has a neuroprotective effect without the development of tolerance.* Neuropharmacology, 2007. **52**(4): p. 1079-1087.
55. Katsidoni, V., I. Anagnostou, and G. Panagis, *Cannabidiol inhibits the reward-facilitating effect of morphine: Involvement of 5-HT1A receptors in the dorsal raphe nucleus.* Addiction Biology, 2013. **18**(2): p. 286-296.
56. French, E.D., K. Dillon, and X. Wu, *Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra.* Neuroreport, 1997. **8**(3): p. 649-652.
57. Vann, R.E., et al., *Divergent effects of cannabidiol on the discriminative stimulus and* place conditioning effects of Δ9-*tetrahydrocannabinol.* Drug and Alcohol Dependence, 2008. **94**(1-3): p. 191-198
58. Klein, C., et al., Cannabidiol potentiates Δ 9-*tetrahydrocannabinol (THC) behavioural effects and alters THC pharmacokinetics during acute and chronic treatment in adolescent rats.* Psychopharmacology, 2011. **218**(2): p. 443-457.

59. Jarbe, T.U.C., B.G. Henriksson, and G.C. Ohlin, Δ9-*THC as a discriminative cue in* pigeons: effects of Δ8-*THC, CBD, and CBN.* Archives Internationales de Pharmacodynamie et de Therapie, 1977. **228**(1): p. 68-72.
60. Haney, M., et al., *Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis.* Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 2016. **41**(8): p. 1974-1982.
61. Babalonis, S., et al., *Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers.* Drug and alcohol dependence, 2017. **172**: p. 9-13.
62. Do Val-da Silva, R.A., et al., *Protective effects of cannabidiol against seizures and neuronal death in a rat model of mesial temporal lobe epilepsy.* Frontiers in Pharmacology, 2017. **8**.
63. Mechoulam, R. and E. Carlini, *Toward drugs derived from cannabis.* Naturwissenschaften, 1978. **65**(4): p. 174-179.
64. Cunha, J.M., et al., *Chronic administration of cannabidiol to healthy volunteers and epileptic patients.* Pharmacology, 1980. **21**(3): p. 175-185.
65. Ames, F. and S. Cridland, *Anticonvulsant effect of cannabidiol.* South African medical journal= Suid-Afrikaanse tydskrif vir geneeskunde, 1986. **69**(1): p. 14-14.
66. Trumbly, B. *Double-blind clinical study of cannabidiol as a secondary anticonvulsant*. in *Presented at Marijuana'90 Int. Conf. on Cannabis and Cannabinoids, Kolympari (Crete)*. 1990.
67. Devinsky, O., et al., *Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.* The Lancet Neurology, 2016. **15**(3): p. 270-278.
68. Devinsky, O., et al., *Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.* New England Journal of Medicine, 2017. **376**(21): p. 2011-2020.
69. Thiele, E.A., et al., *Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial.* Lancet, 2018. **391**(10125): p.1085-1096.
70. Geffrey, A.L., et al., *Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy.* Epilepsia, 2015. **56**(8): p. 1246-1251.
71. Devinsky, O., et al., *Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders.* Epilepsia, 2014. **55**(6): p. 791-802.
72. Pisanti, S., et al., *Cannabidiol: State of the art and new challenges for therapeutic applications.* Pharmacol Ther, 2017. **175**: p. 133-150.
73. Yeshurun, M., et al., *Cannabidiol for the prevention of Graft-versus-Host-Disease after allogeneic hematopoietic cell transplantation: Results of a Phase II study.* Biol Blood Marrow Transplant, 2015. **21**(10): p. 1770-5.
74. McGuire, P., et al., *Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial.* Am J Psychiatry, 2018. **175**(3): p. 225-231.
75. Irving, P.M., et al., *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, 2018. **24**(4): p.714-724.
76. Cunetti, L., et al., *Chronic pain treatment with cannabidiol in kidney transplant patients in Uruguay.* Transplant Proc, 2018. **50**(2): p. 461-464.
77. Hundal, H., et al., *The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group.* J Psychopharmacol, 2018. **32**(3): p. 276-282.
78. Prud'homme, M., R. Cata, and D. Jutras-Aswad, *Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence.* Substance abuse: research and treatment, 2015. **9**: p. 33.
79. World Health Organisation. *WHO Model Lists of Essential Medicines*. March 2017 21 August 2017]; Available from: http://www.who.int/medicines/publications/essentialmedicines/en/.
80. Echo Pharmaceuticals B.V. *Improved uptake of cannabinoid based medicine*. Available

from: http://www.echo-pharma.com/en/about-us/news/improved-uptake-of- cannabinoid-based-medicine
81. Zynerba® Pharmaceuticals. Available from: http://zynerba.com/.
82. Bionorica/THC Pharma. Available from: http://www.cannabidiol-solutions.com/production-process/.
83. Morgan, C.J., et al., *Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings.* Addict Behav, 2013. **38**(9): p. 2433-2436.
84. Arndt, D.L., and H. de Wit, *Cannabidiol does not dampen responses to emotional stimuli in healthy adults.* Cannabis and Cannabinoid Research, 2017. **2**(1): p.105-113.
85. Atsmon, J., et al., *Single-dose pharmacokinetics of oral cannabidiol following administration of PTL101: A new formulation based on gelatin matrix pellets technology*. Clin Pharm Drug Dev, 2017. doi: 10.1002/cpdd.408.
86. Ananda Scientific. Available from: https://www.anandascientific.com/.
87. GW pharmaceuticals. *GW Pharmaceuticals Receives FDA Fast Track and EMA Orphan Designations for Intravenous Cannabidiol in the Treatment of Neonatal Hypoxic-Ischemic Encephalopathy (NHIE)*. 6 August 2015 11 August 2017]; Available from: https://www.gwpharm.com/about-us/news/gw-pharmaceuticals-receives-fda-fast-track-and-ema-orphan-designations-intravenous.
88. European Medicines Agency. *EU/3/15/1520 orphan designation for cannabidiol for the treatment of perinatal asphyxia*. 28 July 2015 10 August 2017]; Available from:http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2015/08/human_orphan_001612.jsp&mid=WC0b01ac058001d12b.
89. Mohammed, N., et al., *Neuroprotective Effects of Cannabidiol in Hypoxic Ischemic Insult. The Therapeutic Window in Newborn Mice.* CNS & Neurological Disorders - Drug Targets- CNS & Neurological Disorders), 2017. **16**(1): p. 102-108.
90. Bonn-Miller, M.O., et al., *Labeling accuracy of cannabidiol extracts sold online.* JAMA, 2017. **318**(17): p. 1708-1709.
91. U.S. Food and Drug Administration. Warning Letters and Test Results for Cannabidiol-Related Products. Available from: https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm.
92. GW pharmaceuticals. *Sativex*. 2016 10 August 2017]; Available from: https://www.gwpharm.com/products-pipeline/sativex
93. Medical Marijuana Inc. *What is cannabidiol?* 11 October 2016 20 August 2018]; Available from: http://www.medicalmarijuanainc.com/what-is-cannabidiol/.
94. Canabidol™ The Best Selling CBD Supplement in Europe. *CBD cannabis oil*. 20 August 2017]; Available from: https://canabidol.com/.
95. United Nations Office on Drugs and Crime. *International Drug Control Conventions*. [cited 21 August 2017; Available from: https://www.unodc.org/unodc/en/commissions/CND/conventions.html.
96. Medicines and Healthcare products Regulatory Agency. 1 August 2017]; Available from: https://www.gov.uk/government/news/mhra-statement-on-products-containing-cannabidiol-cbd
97. Government of Canada Justice Laws Website. 1 August 2017]; Available from: http://laws-lois.justice.gc.ca/eng/acts/c-38.8/FullText.html.
98. Australian Government Department of Health Therapeutic Goods Administration. 1August 2017]; Available from: https://www.tga.gov.au/book/part-final-decisions- matters-referred-expert-advisory-committee-2.
99. New Zealand Government Ministry of Health. 6 September 2017]; Available from: http://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/medicinal-cannabis/cbd-products.
100. Swiss Agency for Therapeutic Products. 1 August 2017]; Available from: https://www.swissmedic.ch/aktuell/00673/03778/index.html?lang=en