CANNABIDIOL (CBD)

Pre-Review Report

Agenda Item 5.2

Expert Committee on Drug Dependence

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World Health Organization

Contents

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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.

CBD can be converted to tetrahydrocannabinol (THC) under experimental conditions; however, this does not appear to occur to any significant effect in patients undergoing CBD treatment.

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®) currently in Phase III trials. 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

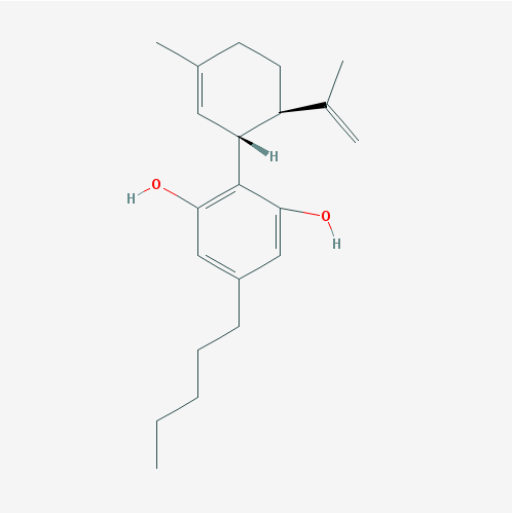
Cannabidiol has not been previously pre-reviewed or critically reviewed by the WHO Expert Committee on Drug Dependence (ECDD). The current review is based on the recommendation from the 38th ECDD that pre-review documentation on cannabis-related substances, including cannabidiol, be prepared and evaluated at a subsequent committee meeting[3].

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 synthesised [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.

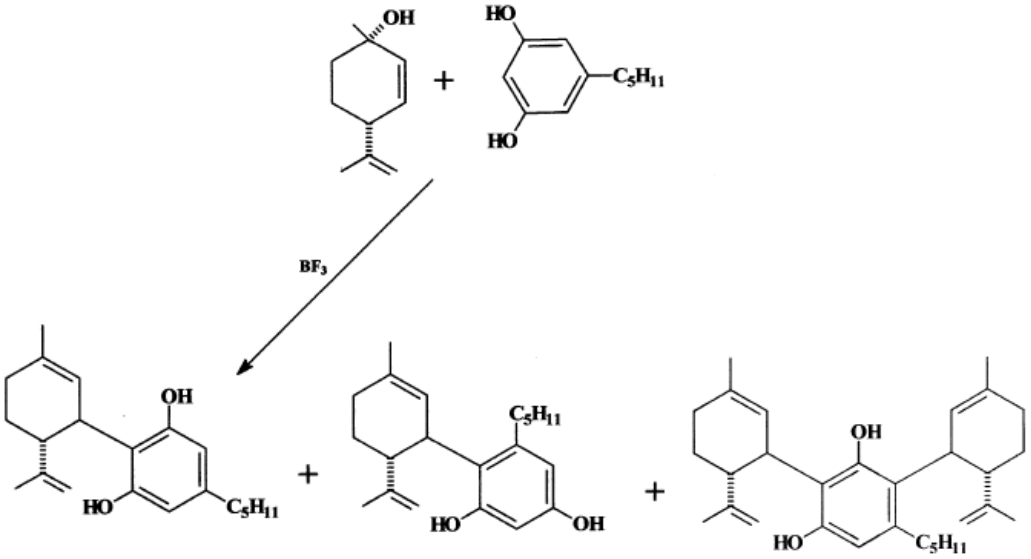
D. Methods and Ease of Illicit Manufacturing

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]



CBD (major product)

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]

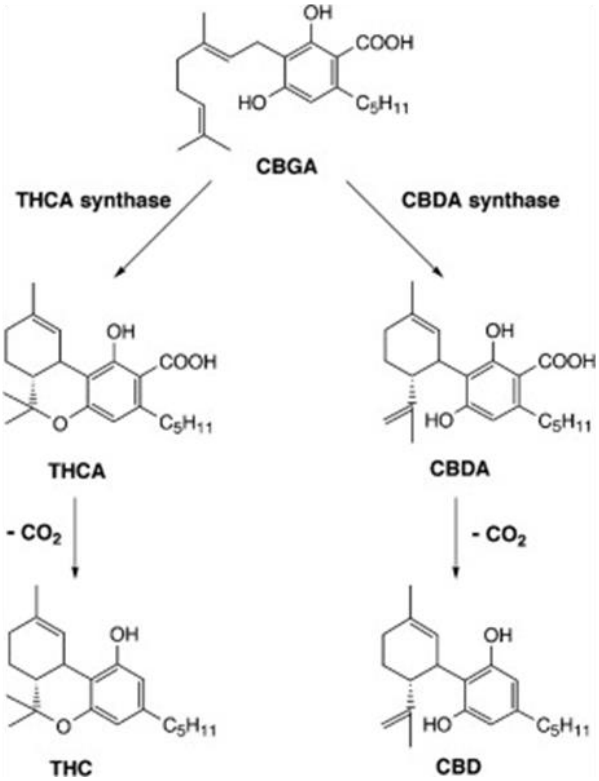


Figure 2: Biogenesis of THC and CBD adapted from Taura et al. (2007) THCA synthase and CBDA synthase catalyze oxidative cyclization of the monoterpene moiety of CBGA to form THCA and CBDA, respectively. THC and CBD are generated from THCA and CBDA by non-enzymatic decarboxylation. [11]

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 and there has been some investigation into whether this occurs spontaneously *in vivo*.

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 version of this method has been reported on a drug user forum. It suggests dissolving CBD in sulphuric acid/acetic acid and leaving it for anywhere from 3 hours to 3 days to obtain delta-9-THC and delta-8-THC. After 3 hours, the author states that CBD has been converted into 52% delta-9-THC and 2% delta-8-THC [31].

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

It has been proposed that the conversion of CBD to delta-9-THC in the presence of acid could occur in the human gut. Such conversion could be of importance if CBD is administered orally. Two *in vitro* studies have used simulated gastric fluid to demonstrate the potential for this conversion. The first reported the formation of analytically confirmed delta-9-THC and delta-8-THC when CBD was exposed to simulated gastric fluid without enzymes at 37ºC. The authors concluded that that the acidic environment during normal gastrointestinal transit could expose orally CBD-

treated patients to levels of THC and other psychoactive cannabinoids that may exceed the threshold for a physiological response. [30] The second *in vitro* study also 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%. [31]

The predictive value of these *in vitro* studies for humans administering cannabidiol orally has been questioned as simulated gastric fluid does not exactly replicate physiological conditions in the stomach. [32] Furthermore, spontaneous conversion of CBD to delta-9-THC has not been demonstrated in humans undergoing CBD treatment. For example, in a six week clinical study in Huntington's disease patients who were administered CBD 700 mg/day, the CBD average plasma concentration range was 5.9-11.2 ng/mL with no delta-9-THC detected. [33]

In humans, THC effects are characterised by impairment of psychomotor and cognitive performance, and a range of physical effects including increased heart rate and dry mouth. In general, clinical studies have reported that even high doses of oral CBD do not cause the those effects that are characteristic for THC and for cannabis rich in THC.[34] For example, in a study of healthy volunteers administered 200mg oral CBD, CBD did not produce any impairments of motor or psychomotor performance.[35] A number of other studies involving high doses of CBD were recently summarized by Grotenhermen et al.[34]; they concluded that high doses of oral CBD consistently fail to demonstrate significant effects or demonstrate effects opposite to those of THC.

While it has been suggested that further large-scale human studies are needed to explore the gastric conversion and potential THC-like side effects following oral CBD administration [36], it is very unlikely that oral cannabidiol will be shown to result in THC concentrations sufficient to induce any meaningful effects.

4. General Pharmacology

A. Routes of administration and dosage

Currently there are no approved marketed pure CBD medicinal products, although two 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. [37]

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.[38] 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. [39] Aerosolized 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. [37, 40]

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.[38] 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. [41]

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 CB1 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. [42]

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. [43, 44] Neuroimaging studies in humans and animals have shown that CBD has effects which are generally opposite to those of THC.[45] 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.[46] 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.[42, 47]

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, 41]

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 mechanism include [48]:

- 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 [49] with a recent update of the literature. [50] 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 (eg, 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.[39] 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. [37, 50] 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. [51] 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.[52]

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. [53]

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.[54] 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. [55] 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 [54]. CBD also failed to substitute for THC in pigeons trained to discriminate THC from vehicle. [56]

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.[39] 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.[57]

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. [58]

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. [59] These studies demonstrated the anti-seizure activity of cannabidiol in a number of animal models. Based on this research, cannabidiol has been trialled 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. [60]

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.[61]

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. [62] 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. [63]

The results of two 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%]). [64]

The same research group recently 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.[65]

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. [66]

It has been suggested that cannabidiol (as Epidiolex) is likely to be submitted for regulatory approval by GW Pharmaceuticals for epilepsy treatment in 2017 following the successful outcomes reported in treatment of Dravet syndrome.

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.[37, 50, 67] The evidence for CBD's various therapeutic applications was recently reviewed by Pisanti et al (2017), refer to Table 1.

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. [68]

Table 1. Overview of diseases for which CBD may have therapeutic benefits taken from Pisanti et al (2017) [69]

Disease	Effects
Alzheimer's disease	Antinflammatory, antioxidant, antiapoptotic in *in vitro* and *in vivo* models of Aβ-evoked neuroinflammatory and neurodegenerative responses.
Parkinson's disease	Attenuation of the dopaminergic impairment *in vivo*; neuroprotection; improvement of psychiatric rating and reduction of agitation, nightmare and aggressive behaviour in patients.
Multiple sclerosis	Improved signs of EAE in mice, antinflammatory and immunomodulatory properties.
Huntington's disease	Neuroprotective and antioxidant in mice transgenic models; no significant clinically important differences in patients.
Hypoxia-ischemia injury	Short term neuroprotective effects; inhibition of excitotoxicity, oxidative stress and inflammation *in vitro* and in rodent models.
Pain	Analgesic effect in patients with neuropathic pain resistant to other treatments.
Psychosis	Attenuation of the behavioural and glial changes in animal models of schizophrenia; anti-psychotic properties on ketamine-induced symptoms
Anxiety	Reduction of muscular tension, restlessness, fatigue, problems in concentration, improvement of social interactions in rodent models of anxiety and stress; reduced social anxiety in patients.
Depression	Anti-depressant effect in genetic rodent model of depression.
Cancer	Antiproliferative and anti-invasive actions in a large range of cancer types; induction of autophagy-mediated cancer cell death; chemopreventive effects.
Nausea	Suppression of nausea and conditioned gaping in rats
Inflammatory diseases	Antinflammatory properties in several in vitro and in vivo models; inhibition of inflammatory cytokines and pathways.
Rheumatoid arthritis	Inhibition of TNF-α in an animal model
Infection	Activity against methicillin-resistant *Staphylococcus aureus*
Inflammatory bowel and Crohn's diseases	Inhibition of macrophage recruitment and TNF-α secretion *in vivo* and *ex vivo*; reduction in disease activity index in Crohn's patients.
Cardiovascular diseases	Reduced infarct size through anti-oxidant and anti-inflammatory properties *in vitro* and *in vivo*.
Diabetic complications	Attenuation of fibrosis and myocardial dysfunction

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).[70]

11. Marketing Authorizations (as a Medicinal Product)

CBD is present in nabiximols (Sativex®) which is marketed by GW Pharmaceuticals in a number of countries. [71] As nabiximols also contains an equal amount of THC, it will be covered in a separate ECDD review.

There are no currently authorized pure CBD products. However, there are several in development including Epidiolex® and Arvisol®.

Epidiolex® is a liquid formulation of pure plant-derived CBD. It is produced by GW Pharmaceuticals 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. [72], [73]

Arvisol® is an oral tablet containing pure CBD. It has been developed by Echo Pharmaceuticals in the Netherlands and is intended to be registered in the treatment of disorders such as schizophrenia and epilepsy. Arvisol® is still undergoing Phase I clinical trials and is not yet available as a medicinal product. [74]

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).[75] The European Commission also granted orphan designation (EU/3/15/1520) for cannabidiol to be used in the treatment of perinatal asphyxia.[76] 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. [77]

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.[78, 79] 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 refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit Production, Consumption and International Trade

Licit production of CBD for medical purposes is described in Section 11. Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit Manufacture and Traffic and Related Information

There are no published statistics (e.g. country data on seizures of illicit CBD) currently available. Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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.[80]

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. [81]

United States: CBD is one of many cannabinoids present in cannabis, and as such is in schedule I of the Controlled Substances Act. However in December 2015, the FDA eased the regulatory requirements to allow researchers to conduct CBD trials. The Drug Enforcement Agency (DEA) stated that these modifications are intended to streamline the research process regarding CBD's possible medicinal value and help foster ongoing scientific studies. [82]

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. [83]

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.[84]

New Zealand CBD is a controlled drug, however many of the restrictions currently imposed by the regulations will be removed by the end of 2017. 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. [85]

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. [86]

Also refer to 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

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of Cannabidiol

Please refer to separate Annex 1 document published on ECDD website