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Toxicological properties of Δ9-tetrahydrocannabinol and cannabidiol

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Cannabis sativa L. contains more than 100 phytocannabinoids that can interact with cannabinoid receptors CB_1 and CB_2. None of the cannabinoid receptor ligands is entirely CB_1- or CB_2-specific. The effects of cannabinoids therefore differ not just because of different potency at cannabinoid receptors but also because they can interact with other non-CB_1 and non-CB_2 targets, such as TRPV1, GPR55, and GPR119. The most studied phytocannabinoid is Δ9-tetrahydrocannabinol (THC). THC is a partial agonist at both cannabinoid receptors, but its psychotomimetic effect is produced primarily via activation of the CB_1 receptor, which is strongly expressed in the central nervous system, with the noteworthy exception of the brain stem. Although acute cognitive and other effects of THC are well known, the risk of irreversible neuropsychological effects of THC needs further research to elucidate the association. Unlike THC, phytocannabinoid cannabidiol (CBD) does not appear to have psychotomimetic effects but may interact with some of the effects of THC if taken concomitantly. CBD administered orally has recently undergone well-controlled clinical trials to assess its safety in the treatment of paediatric epilepsy syndromes. Their findings point to increased transaminase levels as a safety issue that calls for postmarketing surveillance for liver toxicity. The aim of this review is to summarise what is known about acute and chronic toxicological effects of both compounds and address the gaps in knowledge about the safety of exogenous cannabinoids that are still open.

KEY WORDS: acute toxicity; animal studies; cannabidiol; CB_1; CB_2; CBD; chronic toxicity; clinical trials; Δ9-tetrahydrocannabinol; phytocannabinoids; THC

With the growing interest in the use of cannabinoids for medicinal purposes grows a need for a systematic review of their toxicological properties. There are still many uncertainties and contradictions remaining from the increasing number of published cannabinoid safety studies. This is because these studies vary to extremes in their methodology and quality, rendering results difficult to compare. Moreover, toxicity is not systematically covered, and there are no chronic toxicity data from well-defined exposure settings. Higher quality toxicological data are available for cannabinoid-based medicines that are manufactured today as approved drugs. However, the main indications for their use are serious and/or rare diseases, mostly after all other treatment has failed, so their toxicological profile is less detailed than that of the drugs of first choice (1).

Cannabinoid receptor ligands are a varied group of over 100 chemical compounds isolated from *Cannabis sativa* L. (2). The best-characterised cannabinoids found in the cannabis plant are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). They can interact with two types of cannabinoid receptors – cannabinoid type 1 (CB_1) and cannabinoid type 2 (CB_2) – that both belonging to the superfamily of G protein-coupled, seven-transmembrane (7TM) domain receptors (3). None of the cannabinoid receptor ligands, however, are entirely CB_1- or CB_2-specific. Each of these ligands therefore differs in effect, not only because they have different potency at cannabinoid receptors but also because they can interact with other non-CB_1/non-CB_2 targets, such as transient receptor potential channel, vanilloid subfamily member 1 (TRPV1, aka capsaicin or vanilloid receptor), G protein-coupled receptors (GPR55 and GPR119), voltage-gated ion channels, and neuronal transporters of catecholamines (4–6). Despite such diversity, there are only four cannabinoid-based medicines currently on the market: nabiximols (Sativex®), nabilone (Cesamet® or Canemes®), dronabinol (Marinol® or Syndros®), and cannabidiol (Epidiolex®) (7). Still being developed are selective synthetic cannabinoid receptor agonists, antagonists, and modulators, metabolism inhibitors [such as fatty acid amide hydrolase (FAAH) inhibitors] or inhibitors of endocannabinoid reuptake (8).

The aim of this review is to summarise what is known about acute and chronic cannabinoid toxicity, primarily based on animal and clinical studies of medicinal product safety (9). Particular attention will be paid to identifying future studies that could fill in current gaps in knowledge

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and uncertainties surrounding the safety of exogenous cannabinoids. This review will discuss the toxicology of chemically defined, single compounds that are either synthetic, semisynthetic, or plant-derived. We will also discuss why the combination of THC with CBD has fewer adverse effects than THC alone.

What this review will not discuss is the toxicology of medicinal or recreational cannabis use or the health issues associated with contaminants in plant extracts obtained from uncontrolled sources.

CANNABINOID RECEPTORS

THC shares the ability of endocannabinoid ligands anandamide (AEA) and 2-arachidonoylglycerol to activate both the CB_1 and CB_2 receptor. It is their partial agonist, as it binds to them with Ki values in the low nanomolar range. Both receptors are coupled through $G_{i/o}$ proteins, negatively to adenylate cyclase and positively to mitogen-activated protein kinase (3). CB_1 receptors are mainly located at the terminals of central and peripheral neurons, where they usually mediate inhibition of neurotransmitter release. CB_1 is one of the G protein-coupled receptors expressed at the highest level in the central nervous system, with the notable exception of the brain stem (4, 10). This may be why THC is not associated with sudden death due to respiratory depression, which indicates its low acute toxicity. In the brain, CB_1 receptors are particularly concentrated in the hippocampus and cerebral cortex (areas involved in memory and cognition), olfactory areas, basal ganglia and cerebellum (areas involved in motor activity and posture control), hypothalamus (area involved in appetite regulation and energy homeostasis), limbic cortex (area involved in sedation), and neocortex (area involved in the executive function). CB_1 is also found in peripheral nervous organs (lungs, liver, bowel, thyroid, uterus, placenta, and testicles). Therefore, these sites can also be the targets of cannabinoid effects. CB_2 receptors are primarily associated with cells governing the immune function, such as splenocytes, macrophages, monocytes, microglia, and B- and T-cells. Recently, CB_2 receptors have also been reported in other cells, often up-regulated under pathological conditions (5). The functions of these receptors include modulation of cytokine release and immune cell migration. CB_2 receptors are expressed in the brain by microglia, blood vessels, and by some neurons (4, 10). However, their action has not been elucidated.

In contrast to THC, CBD does not seem to be psychoactive and has low affinity for CB_1 and CB_2 receptors (4). This is why its research has focused on non-CB_1/non-CB_2 targets (see THC/CBD interactions below). When interpreting the effects of cannabinoids, we should bear in mind that cannabinoid receptors are members of the rhodopsin-like family of 7TM receptors, at which, according to Kenakin (11), the efficacy of agonist depends on cell type and its condition. Therefore, it is difficult to predict the therapeutic behaviour of cannabinoid receptor agonists. This is probably why higher release of endocannabinoids can be protective in one and damaging in another case.

TOXICOLOGICAL PROPERTIES OF THC

Apart from natural THC, the most reliable toxicological data available to date are for synthetic THC dronabinol and synthetic THC analogue nabilone. Nabilone has a similar chemical structure and is twice as potent as THC at the CB_1 and CB_2 receptors (12). The main indication for dronabinol and nabilone is nausea and vomiting in adult patients receiving chemotherapy when conventional antiemetics fail to do the job. Dronabinol is also indicated for anorexia in adults with AIDS. There are no safety profiles for dronabinol and nabilone in paediatric (<18 years) and elderly (>65 years) populations. The starting dose of dronabinol is 2.5 mg, administered twice daily as capsules for oral use. The maximum recommended dosage is 20 mg/day (4–6 doses a day). Dronabinol is also administered as a 5 mg/mL oral solution. The usual nabilone dose is 1 or 2 mg twice a day, and the maximum recommended dosage is 6 mg/day, administered as capsules for oral use (13, 14). Since both are used short-term, data on chronic effects in humans are not available.

Pharmacokinetics/toxicokinetics of THC

The bioavailability of dronabinol is low (4–20 %) because of its high lipid solubility and extensive first-pass hepatic metabolism (15, 16). Its effects do not show clear dose dependence (17). Due to lipid solubility, the apparent volume of distribution is high (10 L/kg). Dronabinol is extensively metabolised in the liver, primarily by cytochrome P450 enzymes CYP2C9 and CYP3A4. CYP2C9 is probably responsible for the formation of the primary active metabolite hydroxy-Δ^9-THC. Pharmacogenomics studies indicate two to three times higher plasma THC in individuals with a less active form of CYP2C9, so adverse drug reaction in these individuals may be more frequent and/or severe. The major route of excretion is faeces (65 %), and the minor is urine (20 %) (16). Urinary metabolites of dronabinol are identical to those of marijuana and may be excreted over long time (18).

Nabilone has better bioavailability (at least 60 %) than dronabinol and demonstrates dose linearity (15, 19). Multiple cytochrome P450 enzymes extensively metabolise nabilone to various metabolites, which have not been fully characterised yet. Two major metabolic pathways are probably involved in the biotransformation of nabilone: 1) enzymatic reduction of the 9-keto group to form carbinol metabolites; and 2) direct enzymatic oxidation of the aliphatic side-chain to produce carboxylic and hydroxylic analogues. The formation of carbinol metabolites is a major

nabilone metabolic pathway in dog. Hydroxylic analogues appear to be more important in rhesus monkey and man. Carbinols are long-lived metabolites that accumulate in the plasma and concentrate in the brains of treated dogs over time (see chronic toxicity) (20). Nabilone and its metabolites are primarily eliminated in faeces (~65 %) and to a lesser extent in urine (~20 %) (14, 17). Although no accumulation of nabilone was observed after repeated doses, some accumulation was observed for its metabolites (21).

Non-clinical toxicity of THC

Acute oral toxicity of THC in rats is lower in males (LD_{50}=1910 mg/kg) than in females (LD_{50}=1040 mg/kg) (22). The LD_{50} of oral nabilone is >1000 mg/kg in rats of both sexes (21). The signs of acute toxicity of THC and nabilone are similar and include lower respiratory rate, ataxia, decreased activity, catatonia, hypothermia, hypersensitivity to touch, and generalised body twitching. Death was reported to be due to respiratory arrest (21, 22).

Sub-chronic and chronic effects of THC (5, 15, 50, 150, and 500 mg/kg/day) administered by gavage were assessed in rats in a 13-week study followed by a 9-week recovery period and in a 2-year study (12.5, 25, and 50 mg/kg/day) (23). Briefly, THC-treated rats had lower body weight than controls and exhibited convulsions, hyperactivity, and changes in the reproductive organs of both male and female rats. Reduced body weight was notable even at low dose exposure and was attributed to metabolic changes caused by THC. Weight loss was not associated with lower feed consumption but with increased energy consumption (evidenced by higher plasma corticosterone levels) needed for hyperactivity, adaptation, and detoxification from THC. Convulsions and hyperactivity were observed at all doses. The onset and frequency of convulsions were also dose-related. However, Chan et al. (23) observed no histological changes in brain tissue of rats with a history of THC-related convulsion or seizures. Luthra et al. (24) reported generalised depression, followed by hyperactivity, irritability, aggressiveness, and convulsion in rats treated with THC for 119 days. The highest dose of THC in a sub-chronic study in rats induced testicular atrophy and uterine and ovarian hypoplasia (23). This study also found higher serum FSH and LH at all doses.

Nabilone was assessed in two chronic toxicity studies (21). The one in beagle dogs (0.5, 1.0, 2.0 mg/kg/day) was planned to last one year but was terminated after seven months due to high mortality. Most deaths were preceded by convulsions, and toxicity was attributed to accumulation of carbinol metabolites in the brain over time. In contrast to dogs, nabilone chronic toxicity was minimal in rhesus monkeys receiving doses of up to 2.0 mg/kg/day for one year. Transient periods of anorexia, emesis, and ataxia were observed only at the highest dose.

Chan et al. (23) also evaluated THC carcinogenicity in rats and mice and found no evidence in rats at doses of up to 50 mg/kg/day [~20 times the maximal human recommended dose (MHRD)]. In mice, THC produced thyroid follicular cell adenoma (a common benign neoplasm of the thyroid) in both sexes, but the effect was not dose-dependent, as the hyperplasia was increased compared to control at all doses and in both sexes. It is unclear what these findings mean. Carcinogenicity studies have not been performed with nabilone.

Genotoxicity

THC and nabilone have no mutagenic potential (11–13, 23). Positive Ames and skin test results in mice for THC in some *in vitro* tests are attributed to cytotoxic rather than mutagenic action (25).

Reproductive toxicity

THC was evaluated in an oral embryo-foetal developmental study in rats (at doses ranging from 12.5 to 50 mg/kg/day) (26) and in rabbits (0.5, 1.5, 5 and 15 mg/kg/day) (27). No teratogenic effects were observed in rats. Increased foetal mortality and early resorption were associated with maternal toxicity, which manifested itself as lower weight gain. In rabbits, one third of the foetuses in the high-dose group had multiple anomalies (such as acrania and spina bifida). In a single-generation reproductive study (28), male and female rats received 0.5, 1.5, and 5 mg/kg/day of THC by gavage. Offspring to mothers receiving 1.5 and 5 mg/kg/day showed a dose-related drop in survival at day 12 of lactation and at weaning.

A reproduction study of nabilone in rats (1.4, and 12 mg/kg/day) and rabbits (0.7, 1.6, and 3.3 mg/kg/day) (29) showed no teratogenic effects. However, it did find dose-related developmental toxicity, such as embryo death, foetal resorption, decreased foetal weight, and disrupted pregnancy. Another study in rats (24) revealed postnatal developmental toxicity of nabilone at 1.4 and 12 mg/kg/day), manifested by smaller litter size and lower survival as well as lower initial body weight and hypothermia in pups from the high-dose group.

There are no sufficient data on pregnancy outcomes in women exposed to dronabinol (THC) or nabilone.

THC toxicity in clinical trials

Safety data on dronabinol come from 10 randomised, double-blind, placebo-controlled clinical trials. In one trial (30) patients with AIDS-related anorexia (N=139) were receiving dronabinol as appetite stimulant (5 mg/day), and in nine trials patients with cancer (N=454) were receiving dronabinol as antiemetic in the dose range of 2.5–40 mg/day (31–39) for no longer than six weeks. The most frequently reported adverse events (33 %) in patients with AIDS were euphoria, dizziness, somnolence, and thinking abnormalities. The most common adverse events in patients receiving the antiemetic dronabinol were drowsiness, dizziness and transient impairment of sensory and

perceptual functions. Patients from both studies (24% in antiemetic and 8% in appetite stimulant) reported dose-related "highs" (elation, laughter, and heightened awareness). The frequency of adverse effects on the central nervous system (CNS) increased with doses, and their severity greatly varied between patients. After oral administration, dronabinol had an action onset of approximately 30 min to one hour and a peak effect at two to four hours (40). Psychoactive effects lasted four to six hours. Other than those affecting the nervous system, the most frequent adverse effects were gastrointestinal (abdominal pain, nausea, and vomiting) and cardiovascular (palpitation, tachycardia, vasodilatation/facial flush) (30–39). The following were the most serious adverse effects of dronabinol: neuropsychiatric, haemodynamic instability, seizure, paradoxical nausea, vomiting, and abdominal pain. Dronabinol should be discontinued in patients experiencing a psychotic reaction or showing cardiovascular effects (tachycardia, transient changes in blood pressure) and used with caution in patients with a history of epilepsy or recurrent seizures (13).

Nabilone has systematically been evaluated in controlled clinical trials that lasted up to nine weeks (41–43). The lowest nabilone dose (2 mg) had a few adverse effects, whereas a 3–5 mg dose closely mirrored dronabinol's (25 mg) effects (18).

THC addiction and dependence

High levels of CB_1 receptors are found in the brain areas that are part of the mesocorticolimbic dopaminergic pathway and are implicated in motivational and reward processes (44). Being partial CB_1 receptor agonists, THC and its analogues should be tested for their addictive potential (45). Many abused drugs that can lead to addiction increase synaptic dopamine levels in the human limbic striatum. The same was reported for THC in human studies in healthy participants (46–48). Dopamine release was small compared to amphetamine, cocaine, alcohol (10–15 %), and nicotine (~10 %).

First studies in monkeys (49, 50) failed to show the rewarding effects of THC, but newer studies with intravenous dronabinol injection (1–6 μg/kg) confirmed it in squirrel monkeys (51, 52). Another widely used predictor of a reinforcing (and therefore addictive) effect is the conditional place preference (CCP) test, in which a compartment in a cage is associated (paired) with a tested substance. Lepore et. al. (53) reported that CCP depended on the dose and intervals between administration and that dronabinol doses of 2 or 4 mg/kg every 24 h produced a reliable shift in favour of the dronabinol-paired compartment.

Reinforcing effects have also been observed in humans (12). Nabilone (4–8 mg/day) and dronabinol (10–20 mg/day) produced stronger marijuana-like subjective effects, such as feeling good, feeling "high", and feeling "stoned" than placebo. Nabilone had a slower onset of the peak subjective effects.

Chronic therapy with dronabinol can lead to physical dependence. One human study (17) showed that dronabinol doses of 210 mg/day (~10 times higher than MHRD) administered for 12 to 16 consecutive days produced withdrawal syndrome within 12 h after discontinuation. Initial symptoms were irritability, insomnia, and restlessness. By hour 24 of discontinuation, withdrawal symptoms intensified to include "hot flashes", sweating, rhinorrhoea, loose stool, hiccoughs, and anorexia. We still do not know whether nabilone can also lead to physical dependence. Patients that participated in clinical trials for up to five days showed no withdrawal symptoms after discontinuation of dosing (54).

TOXICOLOGICAL PROPERTIES OF CBD

As a 99 % pure extract from *C. sativa*, active substance cannabidiol was first approved in June 2018 under proprietary name Epidiolex® (55). The United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) approved it for the treatment of seizures associated with Lennox-Gestaut (LGS) and Dravet syndrome (DS) in patients two years of age or older. Epidiolex® is administered as a 100 mg/mL oral solution. The starting dose is 2.5 mg/kg twice a day and the maximum recommended dose is 10 mg/kg twice a day (20 mg/kg/day) (55, 56). Considering that Epidiolex® has been approved for treatment in children, CBD has become the most extensively toxicologically tested cannabinoid, and thus the most reliable source of toxicological data. However, because of the seriousness of the indications and failure of patients to respond to existing medication, Epidiolex® was approved in spite of certain deficiencies in the safety assessment (e.g., inadequate safety assessment of major human metabolite 7-COOH-CBD). Additional studies listed in Table 1 should therefore be carried out as part of post-marketing surveillance to obtain a complete safety profile of CBD. Furthermore, no clinical trial with Epidiolex® has been conducted in patients older than 55 years, so its safety profile does not cover the elderly population. General recommendation is to start with the lowest dose (56).

Since CBD is derived from *C. sativa*, Table 2 presents a thorough assessment of the abuse and dependence potential of Epidiolex® (4, 57–59). A human study (58) found marginal abuse potential at a higher therapeutic dose (1500 mg/day) and supratherapeutic dose (4500 mg/day), but there is little other evidence that CBD could cause addiction. The results of a human dependence study of CBD were negative (59).

Pharmacokinetics/toxicokinetics of CBD

Plasma CBD concentrations show a nonlinear increase with dose and 6.5 % bioavailability at a 3000-mg dose (60).

Table 1 Recommended post-marketing studies to obtain a complete safety profile of cannabidiol (CBD)

Non-clinical toxicity studies
Toxicity studies with CBD metabolite 7-COOH-cannabidiol in rat:
- embryo-foetal developmental study
- pre- and postnatal developmental study
- juvenile animal toxicity study
- 2-year carcinogenicity study with gavage
Toxicity studies with CBD
- 2-year carcinogenicity study in mouse
- 2-year carcinogenicity study in rat with gavage
Clinical studies
- Potential for chronic liver injury
- Effect on glomerular filtration rate
- Pregnancy outcome study
- QT interval prolongation trial at the maximum tolerable dose
Drug-drug interaction trials in healthy volunteers
CBD effect on the pharmacokinetics of:
- caffeine
- sensitive CYP2B6* and CYP2C9 substrate
- sensitive UGP1A9** and UGTB7 substrate
Strong CYP3A inhibitor effects on pharmacokinetics of CBD
Strong 2C9 inhibitor effects on pharmacokinetics of CBD
Rifampin effects on pharmacokinetics of CBD

* cytochrome P450; ** UDP-glucuronosyltransferase

CBD absorption increases three times with a high-fat meal and six times with new oral delivery system for lipophilic active compounds (61, 62). Its high estimated volume of distribution (18,800—30,959 L) indicates accumulation of CBD in body fat (63). CBD is extensively metabolised in the liver and gut, mainly by the CYP2C19, CYP3A4, UGT1A7, UGT1A9, and UGT2B7 enzymes (64). Drug interaction trials to assess the effect of CBD on these enzymes in healthy volunteers will be conducted during the post-marketing period (Table 1) (55, 56). The metabolism of CBD is very complex, especially in hepatocytes. The main human metabolite is 7-carboxy-cannabidiol (7-COOH-CBD; ~90 % of all drug-related substances measured in the plasma) (64). Its toxicological profile has not been investigated because experimental animals for toxicological studies (mice, rats, and dogs) do not metabolise CBD to a comparable extent as humans (65). The major concern with 7-COOH-CBD could be its reactive acyl-glucuronide (66) The primary excretion route of CBD is through faeces (84 %), followed by urine (8 %) (63).

Non-clinical toxicology of CBD

In a study of acute effects in rhesus monkeys (67), intravenous CBD caused death by respiratory arrest and cardiac failure at doses above 200 mg/kg (LD_{50}=212 mg/kg). At the lower dose of 150 mg/kg, survivors recovered in one to three days, and liver weights increased from 19 to 142 %. In the part of the study investigating subchronic effects (after 90 days of oral administration), the authors reported inhibition of spermatogenesis at the highest oral dose of 300 mg/kg (67).

Animal studies of CBD alone described below make part of the Epidiolex® European Public Assessment Report (EPAR, EMA's scientific monography) (56). To the best of my knowledge, they have not been published and therefore no further detail or original references are currently available. All these studies were conducted in accordance with medicinal product safety standards and protocols and reviewed by the EMA committee (9).

Two oral chronic toxicity studies (referred to in 56) have assessed CBD in Wistar rats (receiving 15, 50, or 150 mg/kg/day for 6 months) and Beagle dogs (receiving 10, 50, 100 mg/kg/day for 9 months). In both species the primary target organ was the liver. Hepatocellular hypertrophy was detected at all doses, accompanied by an increase in alanine transferase (ALT) and alkaline phosphatase (ALP).

A 104-week oral carcinogenicity study in Wistar rats (referred to in 56) revealed no drug-related neoplastic findings. However, the study had several drawbacks, including impure active substance, excessive effect of body weight, and unknown exposure to the two major human metabolites.

The genotoxic potential of CBD was also investigated in a standard battery of tests, but their results were negative for mutagenicity and clastogenicity (referred to in 56).

A full battery of oral reproductive and developmental studies has been conducted with purified CBD. In an embryo-foetal development study in Wistar rats, litter loss was noted at the highest applied dose of 250 mg/kg. In a prenatal and postnatal development study (referred to in 56) rat exposure to the highest doses (150 and 200 mg/kg/day) affected reproductive organs (smaller testes in males, reduced fertility index in females). A high dose of 125 mg/kg also reduced foetal body weight in New Zealand white rabbit, which was related to maternal toxicity. The developmental toxicity in rabbits occurred at maternal plasma concentration similar to human at therapeutic doses (referred to in 56). In rats these concentrations were much higher. No adequate data are available on pregnancy outcome in women exposed to CBD.

A juvenile toxicity study in Wistar rats (referred to in 56) showed neurobehavioral deficits and delayed sexual maturation in males. A no observed effect level (NOAEL) was 150 mg/kg/day.

Clinical toxicology of CBD

Safety data on Epidiolex® were obtained from four randomised, double-blind, placebo-controlled multicentre trials with exposure to CBD doses of 5, 10, and 20 mg/kg/day (68–70). These phase II studies were conducted in 2 to 55 year-old patients with LGS (N=235) and DS (N=88) for up to 14 weeks.

Additional non-controlled safety data have been obtained from an ongoing open-label Phase III study (Study 1415) in LGS and DS patients (N=644), which is being conducted at 38 sites in the USA and Australia. Since this trial is not finished, an interim analysis of long-term safety was conducted (71, 72).

The most common adverse events in CBD-treated patients affected the following systems: CNS (somnolence, sedation), gastrointestinal tract (lower appetite, diarrhoea), liver (higher transaminase), and the lungs (pneumonia). The severity of these events was generally mild to moderate. Diarrhoea, weight loss, higher ALT, and somnolence/sedation/lethargy were all dose-related. There were two serious cases of transaminase elevation, two severe events with rash (one consistent with a hypersensitivity reaction) and three severe cases of appetite loss. The CBD-treated and the placebo group did not differ in the rate of respiratory failure. Children had lower weight, which was associated to a certain extent with appetite loss (68–71).

Treatment with CBD is clearly associated with an increased risk of hepatotoxicity (68–71). Higher doses of CBD and concomitant use of valproate increase the risk of transaminase elevation in patients. Two patients concomitantly treated with valproate experienced toxic

Table 2 Cannabidiol (CBD) abuse potential

TYPE OF STUDY	RESULTS
Receptor binding studies	
- cannabinoid receptors	no significant affinity
- opioid receptors	no significant affinity
Non-clinical studies evaluating general behaviour (similarity to THC)	
- tetrad test	no meaningful abuse related signal
- drug discrimination study	no meaningful abuse related signal
- self-administration study	no meaningful abuse related signal
Clinical studies evaluating efficacy and safety in patients with LGS* or DS*	
- Phase I clinical study	no euphoria or other abuse-related signals
- Phase II/III studies	could not be evaluated***
Phase I human abuse potential (HAP) study (N=40, with 35 completers)	
randomized, double blind, placebo-controlled trial	
subjects: healthy recreational poly-drug users	
positive control: THC (10, 30 mg), alprazolam (2 mg)	
negative control: placebo	
	mean DRUG LIKING SCORE
lower therapeutic dose: 750 mg/day	not significantly different
higher therapeutic dose: 1500 mg/day	significantly different (very small increase)
supra-therapeutic dose: 4500 mg/day	significantly different (very small increase)
Human physical dependence study following chronic administration	
3 days after discontinuation	no withdrawal signs and symptoms

*Lennox-Gastaut syndrome; **Dravet syndrome; ***concomitant use of other seizure drugs and limited capacity of patients

hepatocellular injury, metabolic acidosis, and encephalopathy. There appears to be no pharmacokinetic interaction between CBD and valproate, although a pharmacodynamical interaction is currently being investigated. The potential of CBD to cause chronic liver injury should be evaluated in the post-marketing period (55, 56) (Table 1).

MECHANISMS OF THC/CBD INTERACTIONS

In spite of its low affinity for the CB_1 and CB_2 receptors, CBD can interfere with some THC adverse effects, particularly in the brain, without interfering with the intended THC effects, such as muscle relaxation (73). Understanding pharmacodynamic interactions between THC and CBD can be quite a challenge. CBD is a ligand with very low affinity for the CB_1 receptor but can still increase CB_1 constitutional or endocannabinoid activity (5), which has been confirmed by. thermodynamic findings that CBD increases membrane fluidity and thereby the activity of the CB_1 receptor (74). Another mechanism of action is that CBD increases the levels of primary endocannabinoids AEA and 2-arachidonyl-glycerol (2-AG) (5). CBD may also interfere with THC through interaction with other non-CB_1 receptors and enzymes in the 'expanded endocannabinoid system' (5). In their systematic review McPartland et al. (5) propose several non-CB_1 receptor mechanisms of CBD antagonising or potentiating THC effects. For example, CBD may attenuate the anxiogenic effect of THC by acting as a direct or indirect agonist on serotonin 1A receptors (5-HT_{1A}). In contrast, it can potentiate THC action on CB_1 receptors by reducing peripheral hyperalgesia via TRPV1 channels (75). Sativex®, as a mixture of THC and CBD, consequently provided better antinociception than THC given on its own 76).

In terms of pharmacokinetic CBD/THC interaction, CBD may impair THC hydrolysis by CYP450 enzymes (77). The inhibition of THC metabolism may vary with species, timing of administration (CBD pre-administration *vs* co-administration), and CYP isoenzymes. In rats or mice THC effects are potentiated when CBD is administered 30 min to 24 h before THC but mitigated if co-administered (78). In humans, no pharmacokinetic interactions between THC and CBD at clinically relevant doses have been reported (79). Co-administration of CBD with THC in one study (80) yielded similar maximum plasma levels of THC as when it was administered alone. Whether CBD will antagonise or potentiate THC effects also seems to depend on their administration ratio, and this ratio varies with species (5).

TOXICOLOGY OF CBD+THC COMBINATIONS

The combination of THC and CBD in a 1:1 ratio makes the active substance nabiximols of the cannabinoid-based medicine Sativex® (81). It is an oromucosal spray approved for the treatment of multiple sclerosis-associated spasticity in adult patients when all other treatment has failed. There is no safety profile of nabiximols in children (>18 years) and the elderly, even though clinical trials included patients up to 90 years of age. Elderly patients may be more susceptible to some adverse effects in the CNS. The oromucosal (e.g. sub-lingual) route resolves the problem of variable bioavailability (typically 6 to 20 %) of orally administered cannabinoids due to first-pass metabolism. Each 100 µL spray contains 2.7 mg THC and 2.5 mg CBD. The starting dose is two sprays per day and the maximum dose is 10–12 sprays per day (corresponding to 32.4 mg THC and 30 mg CBD) (81).

A study using a rat model of Huntington's disease showed that nabiximols can up-regulate CB_1 gene expression (82). CBD increases the levels of the primary endocannabinoids AEA and 2-arachidonyl-glycerol (2-AG) (6).

The most common adverse effects of nabiximols in clinical trials conducted in patients with multiple sclerosis were dizziness, fatigue and gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea) (82–92). These adverse effects and poor efficacy were the main reasons for some patients to discontinue therapy (88, 90). In patients with multiple sclerosis the risk of accidental injury may be increased (83, 87, 92–94). There is little evidence of abuse (addiction) or dependence, and the risk of either to develop is small. However, trials to date have mainly used therapeutic doses, and it is possible that supratherapeutic doses could cause addiction and/or dependence (85, 87, 92–94).

CONCLUSION

In spite of uncertainties about the safety of cannabinoids, there are no doubts about the acute neurological and cardiovascular effects of THC. However, THC is not associated with sudden death due to respiratory depression as is the case with opioid analgesics. Long-term cognitive, psychological, and endocrine effects of THC are still being investigated.

As for CBD, it can be toxic to the liver and increases the risk of somnolence and sedation, but the most commonly observed adverse events in controlled clinical trials were mild to moderate. However, these clinical trials included a small number of subjects and some aspects require continued pharmacovigilance. Regardless of different views on the subject, cannabinoid-based medicines need to be assessed just as any other substance in terms of quality, efficacy, and safety.

Conflicts of interest

None to declare.

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REFERENCES

1. Murphy SM1, Puwanant A, Griggs RC; Consortium for Clinical Investigations of Neurological Channelopathies (CINCH) and Inherited Neuropathies Consortium (INC) Consortia of the Rare Disease Clinical Research Network. Unintended effects of orphan product designation for rare neurological diseases. Ann Neurol 2012;72:481–90. doi: 10.1002/ana.23672
2. ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of *Cannabis sativa* L. Prog Chem Org Nat Prod 2017;103:1–36. doi: 10.1007/978-3-319-45541-9_1
3. Pertwee RG. Pharmacological actions of cannabinoids. In: Pertwee RG, editors. Cannabinoids. Handbook of experimental pharmacology. Vol 168. Berlin, Heidelberg: Springer; 2005. p. 1–51.
4. Pertwee RG. The diverse CB_1 and CB_2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. Br J Pharmacol 2008;153:199–215. doi: 10.1038/sj.bjp.0707617
5. McPartland JM, Duncan M, Di Marzo V, Pertwee R. Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol 2015;172:737–53. doi: 10.1111/bph.12944
6. Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M. Clinical and preclinical evidence for functional interactions of cannabidiol and Δ9-tetrahydrocannabinol. Neuropsychopharmacology 2018;43:142–54. doi: 10.1038/npp.2017.209
7. Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. Eur J Intern Med 2018;49:2–6. doi: 10.1016/j.ejim.2018.01.001
8. Cravatt BF, Lichtman AH. Fatty acid amide hydrolase: an emerging therapeutic target in the endocannabinoid system. Curr Opin Chem Biol 2003;7:469–75. doi: 10.1016/S1367-5931(03)00079-6
9. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Annex 1, Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. [displayed 05 March 2020]. Available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
10. Pertwee RG. Emerging strategies for exploiting cannabinoid receptor agonists as medicines. Br J Pharmacol 2009;156:397–411. doi: 10.1111/j.1476-5381.2008.00048.x
11. Kenakin T. New concepts in pharmacological efficacy at 7TM receptors: IUPHAR review 2. Br J Pharmacol 2013;168:554–75. doi: 10.1111/j.1476-5381.2012.02223.x
12. Bedi G, Cooper ZD, Haney M. Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. Addict Biol 2013;18:872–81. doi: 10.1111/j.1369-1600.2011.00427.x
13. Abbott laboratorie, Limited. [N]Marinol® Product Monograph [displayed 14 April 2019]. Available at https://pdf.hres.ca/dpd_pm/00013378.PDF
14. Valeant Canada Limited. [N]Cesamet® Product Monograph [displayed 28 April 2019]. Available at https://pdf.hres.ca/dpd_pm/00007760.PDF
15. Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential. J Ethnopharmacol 2006;21:1–25. doi: 10.1016/j.jep.2006.02.001
16. McGilveray IJ. Pharmacokinetics of cannabinoids. Pain Res Manag 2005;10(Suppl):15A-22A. doi: 10.1155/2005/242516
17. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. Psychopharmacology (Berl) 1999;141:385–94. doi: 10.1007/s002130050848
18. Lile JA, Kelly TH, Hays LR. Substitution profile of the cannabinoid agonist nabilone in human subjects discriminating δ9-tetrahydrocannabinol. Clin Neuropharmacol 2010;33:235–42. doi: 10.1097/WNF.0b013e3181e77428
19. Lemberger L, Rubin A, Wolen R, DeSante K, Rowe H, Forney R, Pence P. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. Cancer Treat Rev 1982;9(Suppl B):17–23. doi: 10.1016/s0305-7372(82)80031-5
20. Sullivan HR, Hanasono GK, Miller WM, Wood PG. Species specificity in the metabolism of nabilone. Relationship between toxicity and metabolic routes. Xenobiotica 1987;17:459–68. doi: 10.3109/00498258709043952
21. Hanasono GK, Sullivan HR, Gries CL, Jordan WH, Emmerson JL. A species comparison of the toxicity of nabilone, a new synthetic cannabinoid. Fundam Appl Toxicol 1987;9:185–97. doi: 10.1016/0272-0590(87)90042-x
22. Thompson GR, Rosenkrantz H, Schaeppi UH, Braude MC. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. Toxicol Appl Pharmacol 1973;25:363–72. doi: 10.1016/0041-008x(73)90310-4
23. Chan PC, Sills RC, Braun AG, Haseman JK, Bucher JR. Toxicity and carcinogenicity of Δ9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice. Fundam Appl Toxicol 1996;30:109–17. doi: 10.1006/faat.1996.0048
24. Luthra UL, Rosenkrantz H, Heyman IA, Braude MC. Differential neurochemistry and temporal pattern in rats treated orally with Δ9-tetrahydrocannabinol for periods up to six months. Toxicol Appl Pharmacol 1975;32:418–31. doi: 10.1016/0041-008X(75)90232-X
25. International Agency for Research on Cancer (IARC). Report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015–2019. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Lyon: IARC; 2014.
26. Fleischman RW, Hayden DW, Naqvi RH, Rosenkrantz H, Braude MC. The embryotoxic effects of cannabinoids in rats and mice. J Environ Pathol Toxicol 1980;4:471–82. PMID: 6255054
27. Haley SL, Wright PL, Plank JB, Keplinger ML, Braude MC, Calendra JC. The effect of natural and synthetic Δ9-

tetrahydrocannabinol on fetal development. Toxicol Appl Pharmacol 1973;25:450.
28. Keplinger ML, Wright RL, Haley SL, Plank JB, Braude MC, Calandra JC. The effect of natural and synthetic Δ9-tetrahydrocannabinol on reproductive and lactation performance in albino rats. Toxicol Appl Pharmacol 1973;25:449.
29. Brigss GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. Philadelphia (PA): Lippincott Williams and Wilkins; 2011.
30. Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. Dronabinol as a treatment for anorexia associated with weight loss in patinets with AIDS. J Pain Symptom Manage 1995;10:89–97. doi: 10.1016/0885-3924(94)00117-4
31. Sallan SE, Zinberg NE, Frei E 3rd. Antiemetic effect of Δ9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med 1975;293:795–7. doi: 10.1056/NEJM197510162931603
32. Frytak S, Moertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connell MJ, Schutt AJ, Schwartau NW. Δ9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. Ann Intern Med 1979;91:825–30. doi: 10.7326/0003-4819-91-6-825
33. Kluin-Neleman JC, Neleman FA, Meuwissen OJ, Maes RA. Δ9-tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancer chemotherapy; a double-blind cross-over trial against placebo. Vet Hum Toxicol 1979;21:338–40. PMID: 516362
34. Lucas VS Jr, Laszlo J. Δ9-tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. JAMA 1980;243:1241–3. doi: 10.1001/jama.1980.03300380021014
35. Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Arch Intern Med 1980;140:1431–3. doi: 10.1001/archinte.140.11.1431
36. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of Δ9-tetrahydrocannabinol and prochlorperazine. N Engl J Med 1980;302:135–8. doi: 10.1056/NEJM198001173020302
37. Neidhart JA, Gagen MM, Wilson HE, Young DC. Comparative trial of the antiemetic effects of THC and haloperidol. J Clin Pharmacol 1981;21(Suppl 1):38S–42S. doi: 10.1002/j.1552-4604.1981.tb02571.x
38. Citron ML, Herman TS, Vreeland F, Krasnow SH, Fossieck BE Jr, Harwood S, Franklin R, Cohen MH. Antiemetic efficacy of levonantradol compared to Δ9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. Cancer Treat Rep 1985;69:109–12. PMID: 2981616
39. Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JL, Hamm J, Salva K, Wiernik PH, Holroyde CP, Hammill S, Shepard K, Plasse T. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Symptom Manage 1991;6:352–9. doi: 10.1016/0885-3924(91)90026-Z
40. May MB, Glode AE. Dronabinol for chemotherapy-induced nausea and vomiting unresponsive to antiemetics. Cancer Manag Res 2016;8:49–55. doi: 10.2147/CMAR.S81425
41. Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer Treat Rev 1982;9(Suppl 2):25–33. doi: 10.1016/s0305-7372(82)80032-7
42. Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE. Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. Cancer Treat Rev 1982;9(Suppl 2):39–44. doi: 10.1016/s0305-7372(82)80034-0
43. Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. Br J Cancer 1983;48:657–63. doi: 10.1038/bjc.1983.247
44. Panagis G, Mackey B, Vlachou S. Cannabinoid regulation of brain reward processing with an emphasis on the role of CB_1 receptors: A step back into the future. Front Psychiatry 2014;5:1–20. doi: 10.3389/fpsyt.2014.00092
45. European Medicines Agency (EMA). Guideline on the non-clinical investigation of the dependence potential of medicinal products [displayed 2 March 2020]. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-investigation-dependence-potential-medicinal-products_en.pdf
46. Brody AL, Mandelkern MA, Olmstead RE, Allen-Martinez Z, Scheibal D, Abrams AL, Costello MR, Farahi J, Saxena S, Monterosso J, London ED. Ventral striatal dopamine release in response to smoking a regular vs a denicotinized cigarette. Neuropsychopharmacology 2009;34:282–9. doi: 10.1038/npp.2008.87
47. Urban NB, Kegeles LS, Slifstein M, Xu X, Martinez D, Sakr E, Castillo F, Moadel T, O'Malley SS, Krystal JH, Abi-Dargham A. Sex differences in striatal dopamine release in young adults after oral alcohol challenge: apositron emission tomography imaging study with [11C]raclopride. Biol Psychiatry 2010;68:689–96. doi: 10.1016/j.biopsych.2010.06.005
48. Bossong MG, Mehta MA, van Berckel BN, Howes OD, Kahn RS, Stokes PR. Further human evidence for striatal dopamine release induced by administration of Δ9-tetrahydrocannabinol (THC): selectivity to limbic striatum. Psychopharmacology (Berl) 2015;232:2723–9. doi: 10.1007/s00213-015-3915-0
49. Harris RT, Waters W, McLendon D. Evaluation of reinforcing capability of Δ9-tetrahydrocannabinol in rhesus monkeys. Psychopharmacologia 1974;37:23–9. doi: 10.1007/bf00426679
50. Mansbach RS, Nicholson KL, Martin BR, Balster RL. Failure of! Δ9-tetrahydrocannabinol and CP 55,940 to maintain intravenous self-administration under a fixed-interval schedule in rhesus monkeys. Behav Pharmacol 1994;5:219–25. doi: 10.1097/00008877-199404000-00014
51. Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat Neurosci 2000;3:1073–4. doi: 10.1038/80577
52. Justinova Z, Tanda G, Redhi GH, Goldberg SR. Self-administration of Δ9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. Psychopharmacology (Berl) 2003;169:135–40. doi: 10.1007/s00213-003-1484-0
53. Lepore M, Vorel SR, Lowinson J, Gardner EL. Conditioned place preference induced by Δ9-tetrahydrocannabinol: comparison with cocaine, morphine, and food reward. Life Sci 1995;56:2073–80. doi: 10.1016/0024-3205(95)00191-8
54. Herman TS, Einhorn LH, Jones SE, Nagy C, Chester AB, Dean JC, Furnas B, Williams SD, Leigh SA, Dorr RT, Moon TE.

Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. N Engl J Med 1979;300:1295–7. doi: 10.1056/NEJM197906073002302
55. Food and Drug Organization (FDA). Center for drug evalution and research. Epidiolex. Summary review [displayed 28 April 2019]. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000SumR.pdf
56. European Medicines Agency (EMA). European Public Assessment report. Epidyolex, [displayed 05 March 2020]. Available at https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
57. Robert EM, Taylor NL, Martin BR, Wiley JL. Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Δ9-tetrahydrocannabinol. Drug Alcohol Depend 2008;94:191–8. doi: 10.1016/j.drugalcdep.2007.11.017
58. Schoedel KA, Szeto I, Setnik B, Sellers EM, Levy-Cooperman N, Mills C, Etges T, Sommerville K. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. Epilepsy Behav 2018;88:162–171. doi: 10.1016/j.yebeh.2018.07.027
59. World Health Organization Expert Committee on Drug Dependence. Cannabidiol (CBD) Pre-Review Report Agenda Item 5.2 and Peer Review, 2017. Available AT https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf
60. Lim SY, Sharan S, Woo S. Model-based analysis of cannabidiol dose-exposure relationship and bioavailability. Pharmacotherapy 2020. doi: 10.1002/phar.2377
61. Zgair A, Wong JC, Lee JB, Mistry J, Sivak O, Wasan KM, Hennig IM, Barrett DA, Constantinescu CS, Fischer PM, Gershkovich P. Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. Am J Transl Res 2016;8:3448–59. PMCID: PMC5009397
62. Cherniakov I, Izgelov D, Domb AJ, Hoffman A. The effect of Pro NanoLipospheres (PNL) formulation containing natural absorption enhancers on the oral bioavailability of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a rat model. Eur J Pharm Sci 2017;109:21–30. doi: 10.1016/j.ejps.2017.07.003
63. Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. Eur J Clin Pharmacol 2013;69:1135–47. doi: 10.1007/s00228-012-1441-0
64. Ujváry I, Hanuš L. Human metabolites of cannabidiol: A review on their formation, biological activity, and relevance in therapy. Cannabis Cannabinoid Res 2016;1:90–101. doi: 10.1089/can.2015.0012
65. Harvey DJ, Samara E, Mechoulam R. Comparative metabolism of cannabidiol in dog, rat and man. Pharmacol Biochem Behav 1991;40:523–32. doi: 10.1016/0091-3057(91)90358-9
66. Regan SL, Maggs JL, Hammond TG, Lambert C, Williams DP, Park BK. Acyl glucuronides: the good, the bad and the ugly. Biopharm Drug Dispos 2010;31:367–95. doi: 10.1002/bdd.720
67. Rosenkrantz H, Fleischman RW, Grant RJ. Toxicity of short-term administration of cannabinoids to rhesus monkeys. Toxicol Appl Pharmacol 1981;58:118–31. doi: 10.1016/0041-008x(81)90122-8
68. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S. Cannabidiol in Dravet syndrome study group. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376:2011–20. doi: 10.1056/NEJMoa1611618
69. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378:1888–97. doi: 10.1056/NEJMoa1714631
70. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:1085–96. doi: 10.1016/S0140-6736(18)30136-3
71. Laux LC, Bebin EM, Checketts D, Chez M, Flamini R, Marsh ED, Miller I, Nichol K, Park Y, Segal E, Seltzer L, Szaflarski JP, Thiele EA, Weinstock A; CBD EAP study group. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. Epilepsy Res 2019;154:13–20. doi: 10.1016/j.eplepsyres.2019.03.015
72. ClinicalTrials.gov database. GWPCARE5 - An Open Label Extension Study of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet or Lennox-Gastaut Syndromes [displayed 4 March 2020]. Available at https://clinicaltrials.gov/ct2/show/record/NCT02224573
73. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses 2006;66:234–46. doi: 10.1016/j.mehy.2005.08.026
74. Howlett AC, Scott DK, Wilken GH. Regulation of adenylate cyclase by cannabinoid drugs. Insights based n thermodynamic studies. Biochem Pharmacol 1989;38:3297–304. doi: 10.1016/0006-2952(89)90628-x
75. Costa B, Giagnoni G, Franke C, Trovato AE, Colleoni M. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br J Pharmacol 2004;143:247–50. doi: 10.1038/sj.bjp.0705920
76. Comelli F, Giagnoni G, Bettoni I, Colleoni M, Costa B. Antihyperalgesic effect of a *Cannabis sativa* extract in a rat model of neuropathic pain: mechanisms involved. Phytother Res 2008;22:1017–24. doi: 10.1002/ptr.2401
77. Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. Drug Metab Dispos 1995;23:825–31. PMID: 7493549
78. Wright MJ Jr, Vandewater SA, Taffe MA. Cannabidiol attenuates deficits of visuospatial associative memory induced by Δ9-tetrahydrocannabinol. Br J Pharmacol 2013;170:1365–73. doi: 10.1111/bph.12199
79. Nadulski T, Pragst F, Weinberg G, Roser P, Schnelle M, Fronk EM, Stadelmann AM. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Δ9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. Ther Drug Monit 2005;27:799–810. doi: 10.1097/01.ftd.0000177223.19294.5c
80. Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral Δ9-tetrahydrocannabinol and oromucosal

cannabis extract administration. Clin Chem 2011;57:66–75. doi: 10.1373/clinchem.2010.152439
81. Medicines and Healthcare Products Regulatory Agency (MHRA). Public Assessment Report. Sativex oromucosal Spray [displayed 28 April 2019]. Available at http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf
82. Sagredo O, Pazos MR, Satta V, Ramos JA, Pertwee RG, Fernández-Ruiz J. Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease. J Neurosci Res 2011;89:1509–18. doi: 10.1002/jnr.22682
83. Vaney C, Heinzel-Gutenbrunner M, Jobin P, Tschopp F, Gattlen B, Hagen U, Schnelle M, Reif M. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler 2004;10:417–24. doi: 10.1191/1352458504ms1048oa
84. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler 2004;10:434–41. doi: 10.1191/1352458504ms1082oa
85. Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler 2006;12:639–45. doi: 10.1177/1352458505070618
86. Collin C, Davies P, Mutiboko IK, Ratcliffe S; Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol 2007;14(3):290–6. doi: 10.1111/j.1468-1331.2006.01639.x
87. Serpell MG, Notcutt W, Collin C. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. J Neurol 2013;260:285–95. doi: 10.1007/s00415-012-6634-z
88. Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, Notcutt W, O'Leary C, Ratcliffe S, Nováková I, Zapletalova O, Piková J, Ambler Z. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res 2010;32:451–9. doi: 10.1179/016164109X12590518685660
89. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, Gasperini C, Pozzilli C, Cefaro L, Comi G, Rossi P, Ambler Z, Stelmasiak Z, Erdmann A, Montalban X, Klimek A, Davies P; Sativex Spasticity Study Group. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol 2011;18:1122–31. doi: 10.1111/j.1468-1331.2010.03328.x
90. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regime, in the relief of central europathic pain in patients with multiple sclerosis. J Neurol 2013;260:984–77. doi: 10.1007/s00415-012-6739-4
91. García-Merino A. Endocannabinoid system modulator use in everyday clinical practice in the UK and Spain. Expert Rev Neurother 2013;13(3 Suppl 1):9–13. doi: 10.1586/ern.13.4
92. Rekand T. THC:CBD spray and MS spasticity symptoms: data from latest studies. Eur Neurol 2014;71(Suppl 1):4–9. doi: 10.1159/000357742
93. Aragona M, Onesti E, Tomassini V, Conte A, Gupta S, Gilio F, Pantano P, Pozzilli C. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. Clin Neuropharm 2009;32:41–7. doi: 10.1097/WNF.0B013E3181633497
94. Robson P. Abuse potential and psychoactive effects of Δ^9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. Expert Opin Drug Saf 2011;10:675–85. doi: 10.1517/14740338.2011.575778

Toksikološke lastnosti kanabinoidov

Iz rastline *Cannabis sativa* L. so do sedaj izolirali že več kot 100 fitokanabinoidov, poleg njih pa obstaja več kot 550 sintetičnih spojin, ki delujejo na kanabinoidne receptorje CB_1 in CB_2. Prav tako je treba omeniti, da nobeden od ligandov kanabinoidnih receptorjev ni popolnoma CB_1- ali CB_2-specifičen. Zato se učinki vsakega od njih razlikujejo ne le zaradi različne moči na kanabinoidnih receptorjih, ampak tudi zato, ker lahko delujejo na druga ne-CB_1 in ne-CB_2 prijemališča. Najpogosteje proučevani kanabinoid je Δ9-tetrahidrokanabinol (THC). THC je delni agonist na obeh kanabinoidnih receptorjih, vendar je njegov psihoaktivni učinek povezan predvsem z aktivacijo receptorjev CB_1. Receptor CB_1 je eden izmed metabotropnih receptorjev z največjo ekspresijo v osrednjem živčevju, z izjemo možganskega debla. Čeprav so akutni učinki na osrednji živčni sistem THC jasno opredeljeni, je tveganje za ireverzibilne nevropsihološke učinke THC kot neodvisnega dejavnika potrebno nadalje raziskati za pojasnitev povezave. Za razliko od THC, fitokanabinoid kanabidiol (CBD) nima psihoaktivnih učinkov, vendar lahko pri sočasni uporabi vpliva na nekatere učinke THC. CBD, ki nima pomembne afinitete za CB_1 in CB_2,, aktivira ali zavira številne uveljavljene in domnevne farmakološke tarče. CBD je kot aktivna snov v zdravilu Epidiolex® pred kratkim opravil nadzorovana klinična preskušanja, da so ocenili njegovo varnost pri zdravljenju redkih epileptičnih sindromov pri otrocih. Največjo zaskrbljenost glede varnosti so predstavljale povišane vrednosti transaminaz. Zato je treba izvesti postmarketinški nadzor toksičnosti za jetra. Članek bo povzel kar je znano o akutnih in kroničnih toksikoloških učinkih, katere študije še manjkajo in kaj so negotovosti v zvezi z varnostjo eksogenih kanabinoidov.

KLJUČNE BESEDE: Δ^9-tetrahidrokanabinol; akutna in kronična toksičnost; kanabidiol; podatki od ljudi; študije na živalih