Cannabidiols/CBD oil
Information for Professionals

Introduction

Cannabis (*Cannabis sativa* plant) contains over 80 different types of cannabinoid compounds. There are variations of the plant – one particular variety of the plant is hemp. Hemp contains little Delta-9-tetrahydrocannabinol (THC), and therefore is grown and used industrially to make various products. The main cannabinoids within the Cannabis plant are:

- Cannabidiol (also known as CBD) – this has no psychoactive properties and is legal to supply, possess and use in the UK. CBD in its pure form is not a controlled substance. However:
    - It is very difficult to isolate pure CBD and is thought that many products in fact do not fully disclose their contents or provide a full spectrum analysis at an appropriate level of sensitivity to accurately and consistently determine their true content or control status
    - If a CBD product contained **any** controlled cannabinoids, unintentionally or otherwise (e.g. THC), then it is highly likely that the product would be controlled
    - For a CBD product to be lawfully available for human consumption it needs to either meet the Exempted Product Criteria in Regulation 2 of the Misuse of Drug Regulations 2001 or the definition of a Cannabis Based Product for Medicinal Use in Humans in Schedule 2 of the Misuse of Drugs Regulation 2001
- Delta-9-tetrahydrocannabinol (THC) – this is a psychoactive compound and is illegal to supply and possess unless it is prescribed in the UK

Since most of the high-street available cannabidiol-containing products are sold as food supplements, they do not fall under the 2012 Human Medicines Regulation's definition of a medicinal product and so are not regulated by the MHRA. Therefore, they are not obliged to meet good manufacturing practice, including safety, quality and efficacy standards. As a result, their safety and quality cannot be guaranteed. Thus, any patient willing to purchase CBD-containing supplement should do so from a reputable source.

Information regarding cannabidiol safety is restricted to a few human studies and case reports. Information should be interpreted with caution. Further studies are needed to evaluate the full safety profile and potential drug interactions.

Formulations of Cannabidiols

Medicinal Products

There are three licensed medicinal products available:

- Sativex (Schedule 4 Part 1 Controlled Drug)
- Nabilone (Schedule 2 Controlled Drug)
- Epidiolex (Schedule 2 Controlled Drug)

None of these products are recommended by National Institute for Health and Care Excellence (NICE) in its Cannabis based medicinal products guidelines for use in chronic pain (see the guideline for further information).

There are a number of unlicensed medicinal products available – the prescribing of these items would need to follow individual organisations' unlicensed medicines policy.

Non-Prescribed Products

There are a number of different formulations of cannabis-based products (non-prescribed) available on the market. Cannabidiol (CBD)-containing products are commonly advertised to be free from tetrahydrocannabinol (THC), however many of these products have the potential to contain traces of THC (due to undisclosed ingredients or variation in content of ingredients), even after the manufacturing process. This is because it is very difficult to isolate CBD oil. This may contribute to potential adverse effects and drug interactions.

These products may be marketed as herbal or food supplements. The variety of products available is vast. This ranges from oral liquid and capsules, to vaping liquids. Products can be bought from pharmacies or health food shops or can be obtained from internet retailers and other sources. The exact composition of these products, although maybe stated on the packaging, is often found to be different than stated – usually less than what is claimed to be in the product. Below is a guide to the onset and duration of effects depending on its formulation.

Onset and duration of action of Cannabis via different routes

*using a vaporising device that blows hot air through finely ground cannabis at a specified temperature
Ref: Pharmaceutical Journal

Uses of cannabidiols

The product Sativex is licensed to be used for moderate to severe spasticity due to multiple sclerosis (MS) and Nabilone is licensed for post chemotherapy nausea and vomiting unresponsive to conventional antiemetics. Epidiolex however is licensed by the European Medicines Agency (EMA) for use in the EU and is now NICE recommended in rare and severe epilepsy (Dravet Syndrome and Lennox-Gastaut Syndrome) – see NICE guideline.

Other uses perceived by patients include (there is insufficient evidence to support these uses):

- Anxiety
- Bipolar disorder
- Epilepsy
- Insomnia
- Schizophrenia
- Pain
- To treat cancer

Adverse effects

Cannabidiol was generally well-tolerated in most trials with a good safety profile, but some mild adverse effects documented included as documented in the table below.

Adverse effects	Cannabidiol	Illicit smoked cannabis
Cardiovascular	Hypotension light-headedness	Angina, myocardial infarction, palpitations, cardiomyopathy, hypertension and tachycardia
Gastrointestinal	Dry mouth, decreased appetite, nausea, diarrhoea	Abdominal pain, diarrhoea, nausea and vomiting
Neurological	Sedation, asthenia, somnolence and psychomotor slowing	Dizziness, anxiety, lethargy, paranoia, hallucinations, impaired concentration, memory loss, suicidal thoughts, mood or behavioural changes, psychosis, seizures, stroke and syncope.
Hepatobiliary	Raised serum aminotransferases (>3 x ULN). This normally occurred within	

	the first 30-90 days of treatment.	
Infections	Pharyngitis and URTI	
Hypersensitivity	Pruritus, erythema and angioedema	
Special senses		Blurred vision, vertigo, altered taste

Healthcare professionals and patients are recommended to report any suspected adverse reactions to CBD oil or cannabis-based medicinal products via the Yellow Card Scheme https://yellowcard.mhra.gov.uk/

Pharmacokinetics

Oral cannabidiol (CBD) is poorly absorbed due to extensive first pass metabolism, whereas inhaled CBD can achieve higher plasma concentrations. Cannabinoids are extensively metabolised in the liver via cytochrome P-450 isoenzymes and primarily excreted by the kidneys. Moderate to severe existing renal and liver impairments could theoretically reduce the clearance and/or excretion of cannabidiol and could increase the risks of side effects occurring. Due to this increased exposure to cannabidiol, dose adjustments may be necessary in patients with moderate or severe hepatic impairment. Cannabidiol is not associated with causing any renal or hepatic impairment.

Pharmacodynamics

CBD has been shown to interact with a number of endocannabinoid and non-endocannabinoid signalling systems. Unlike other cannabinoids, it does not activate cannabinoid 1 and 2 receptors, which is likely to explain the lack of psychotropic effect.

Drug-Drug Interactions

Many studies suggest that cannabinoids are metabolised in the liver by the cytochrome P-450 isoenzymes, mainly CYP-3A4 and CYP-2C19 (CBD) and CYP-

3A4 and CYP-2C9 (THC). Therefore, caution should be taken when co-administered with any medications that are CYP inhibitors or inducers (Table 1).

Table 1 Examples of CYP 450 Isoenzyme Inhibitors and Inducers

CYP-3A4 Inhibitors – decreases metabolism of CBD and THC -> increased CBD and THC concentrations and thus risk of adverse effects	**CYP-2C19 Inhibitors –** decreases metabolism of CBD -> increased CBD concentration and thus risk of adverse effects	**CYP-3A4 Inducers** – increases metabolism of CBD and THC and thus decreases CBD and THC concentration	**CYP-2C19 Inducers -** increases metabolism of CBD and thus decreases CBD concentration
Clarithromycin	Esomeprazole	Carbamazepine	Carbamazepine
Ketoconazole	Omeprazole	Phenytoin	Rifampicin
Itraconazole	Voriconazole	Glucocorticoids	St John's Wort
Diltiazem	Citalopram	Phenobarbital	
Verapamil	Fluoxetine		
Erythromycin	Lansoprazole		
Fluconazole			
Voriconazole			
Grapefruit juice			
Amiodarone			
Ciprofloxacin			
Omeprazole			

Key **- Strong Inhibitor - Moderate Inhibitor - Inhibitor strength level under review - Enzyme Inducer**

Several studies demonstrated that CBD has the potential to inhibit cytochrome P450 isoenzymes in vitro (including CYP 2C19, CYP2C9, CYP2D6 and CYP3 family), however it is not clear that this occurred at concentrations achieved with doses used clinically. Inhibition of these isoenzymes can reduce the metabolism of their substrates (see Table 2) and thus, may increase the risk of side effects and toxicity of substrate – **use with caution**.

CYP-2C19 Substrates	**CYP2C9 Substrates**	**CYP2D6 Substrates**	**CYP3A family Substrates**
Amitriptyline	Amitriptyline	Amitriptyline	Alfentanil
Citalopram	Celecoxib	Citalopram	Amlodipine
Clobazam	Diclofenac	Codeine	Citalopram
Diazepam	Fluoxetine	Duloxetine	Clarithromycin

Lansoprazole	Ibuprofen	Haloperidol	Codeine
Omeprazole	Naproxen	Metoclopramide	Dexamethasone
Phenobarbitone	Tamoxifen	Ondansetron	Diltiazem
Progesterone	Valproic acid	Oxycodone	Domperidone
Propranolol	Venlafaxine	Paroxetine	Fentanyl
Venlafaxine	Voriconazole	Tramadol	Haloperidol
Warfarin	Warfarin		Methadone
			Midazolam
			Risperidone
			Verapamil

Table 2. Examples of CYP450 Isoenzyme Substrates

Cannabinoids also have synergistic effects with CNS depressants (e.g. opioids, hypnotics, sedatives, alcohol) which can lead to increased sedative and hypnotic effects. There is also an increase in the incidence of antimuscarinic side effects e.g. tachycardia, when CBD is given concurrently with tricyclic antidepressants. Other interactions of note include the potential to increase clearance of theophylline (CBD and THC have demonstrated some CYP1A2 inhibition) – ensure levels of theophylline are monitored – may require a dose adjustment.

As there is limited experience with cannabis-based medicinal products, many of these drug interactions are theoretical or have only been demonstrated with in vitro studies. Therefore, it is difficult to recommend detailed action in relation to the potential interactions, other than to advise caution; dose adjustments may be necessary. There are potentially more, undiscovered drug-drug interactions not stated in this document. Different cannabis-based medicinal products will contain varying amounts of THC and CBD which may impact on the interactions observed.

Herbal Interactions

Cannabidiol can increase the incidence of somnolence and sedation in herbal medications that have sedative properties such as calamus, California poppy, catnip, hops, Jamaican dogwood, kava, L-tryptophan, melatonin, sage, St. John's wort, sassafras.

Food Interactions

Taking CBD with a meal that is high in fat increases the amount of cannabidiol that is absorbed by the body. This might increase the effects and side effects of CBD.

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Medicinal Cannabis—Potential Drug Interactions

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