# Cannabidiol oil – potential adverse effects and drug interactions

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## Background

The cannabis plant (*Cannabis sativa)* contains over 100 constituents known as phytocannabinoids. Over the past few decades there has been a vast expansion of research investigating its pharmacological potential. Tetrahydrocannabinol (THC) is responsible for the main psychotropic effect of cannabis. More recently cannabidiol (CBD), a non-psychoactive component, has been researched for its multi-modal properties in various medical conditions (1, 2) CBD contributes up to 40% of the extract of the plant (2); although concentrations of cannabinoids vary depending on the portion of the plant analysed, the plant phenotype and the condition in which it was grown. (3) CBD has been shown to interact with a number of endocannabinoid and non-endocannabinoid signalling systems. It does not activate cannabinoid 1 and 2 receptors unlike other cannabinoids, which is likely to explain its lack of psychotropic effect. (4)

This Q&A focuses on CBD oil, distinct from cannabis-based products for medicinal use, more information on cannabis-based products for members of the public and healthcare professionals can be found on the NHS Choices website and NHS England website, respectively. CBD oil is commonly referred to as hemp seed oil; although they are two distinct products. CBD is typically extracted from flowering buds of the cannabis plant whereas hemp seed oil is derived from cold pressing of cannabis seeds. (5, 6)

Currently, a licensed product containing CBD alone is not available in the UK. However, CBD-containing products are sold as food supplements and are available on the high street. (7) These products do not fall under the Human Medicines Regulations 2012 definition of a medicinal product and are not required to meet good manufacturing practice, including safety, quality and efficacy standards; as a result, the safety and quality of such products may not be guaranteed. CBD-containing products, although commonly advertised to be free from THC, have the potential to contain traces of THC, even after the manufacturing process. (8) Anyone wishing to use a CBD containing supplement should ensure they obtain their supply from a reputable source.

## Answer

A literature search has identified limited human studies on CBD which have used a range of doses from 5-50mg/kg per day. The adverse events identified from these trials have been summarised below. (9-17)

### Adverse effects

The most common adverse effects found in the studies were somnolence, decreased appetite, vomiting and diarrhoea. (10-15) In an open label trial on the use of CBD (n = 162) in patients with treatment resistant epilepsy the following adverse effects occurred in more than 5% of patients: somnolence, decreased appetite, diarrhoea, fatigue, convulsions, appetite changes, status epilepticus, lethargy changes, changes in concentration of concomitant antiepileptic drugs, gait disturbance and sedation. The authors stated that most adverse effects were mild or moderate and transient in nature. Treatment emergent serious adverse effects included: status epilepticus (6%), diarrhoea (2%) and ≤1% of patients had decreased weight, convulsion, decreased appetite, lethargy and pneumonia. (10)

A higher proportion of patients taking clobazam and CBD reported somnolence or fatigue than those taking CBD without clobazam. Five (3%) patients were diagnosed with mild to moderate thrombocytopenia related to CBD use, one (1%) patient had severe thrombocytopenia that resolved

when concomitant valproate was stopped. One (1%) patient taking valproate with CBD developed hyperammonaemia which led to CBD discontinuation. (10)

Elevated transaminase enzymes were observed in 11 (7%) patients, of which one resulted in hepatotoxicity that led to the discontinuation of CBD. All patients that had hepatic or platelet abnormalities were also taking valproate in addition to CBD. (10) Furthermore, a double-blind, placebo-controlled trial (n = 171) on CBD use in Lennox Gastaut syndrome describes raised transaminase and gamma-glutamyltransferase levels in patients that were taking CBD. All elevations resolved either spontaneously during treatment (eight patients in CBD group and one in the placebo group), after a reduction in concomitant valproate dose (three patients in the CBD group), after tapering or cessation of CBD (six patients in CBD group) or after entry into the open label extension trial (three patients in CBD group). (12)

A double-blind, placebo-controlled trial which investigated CBD (n = 60) for the treatment of symptomatic ulcerative colitis found most adverse effects were mild or moderate in severity. Although, three patients had severe neurological adverse effects which included disturbance in attention, dizziness, joint swelling, and muscle twitching. Approximately twice as many patients in the CBD-rich botanical extract group stopped CBD due to adverse events compared to those in the placebo group. It should be noted the CBD administered was not highly purified and contained a number of other excipients including up to 4.7% of THC which could have contributed to some of the adverse effects. (13)

An open-label evaluation of CBD in dystonic movement disorders (n = 5) described the adverse events of CBD to be mild and included hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation. In two patients with coexisting Parkinsonian features, CBD at doses over 300 mg/day exacerbated the hypokinesia and resting tremor. (16)

Finally, in another study (n = 5) CBD was trialled for refractory seizures in Sturge-Weber syndrome, one patient reported eye exotropia and redness. The authors concluded this was possibly related to CBD. (17)

If a patient is self-administering CBD which they have bought over-the-counter, the clinician should be aware of its potential side effects, in particular when prescribing medications that may cause an additive effect.

The information from the trials mentioned should be interpreted with caution as not all studies have carried out statistical analysis to confirm the association between the adverse event and the use of CBD. Moreover, most trials have used highly purified CBD whereas patients may be using a product that contains various other constituents including THC which may also cause its own side effects. Healthcare professionals should make patients aware that low doses of THC can cause psychological effects, such as euphoria, drowsiness, and altered perception of time. Therefore, an individual's ability to drive may be impacted; however, the specific correlation between cannabis blood levels and impairment of driving performance has not yet been established. Regardless of this, the UK government has included cannabis (THC) under drug driving law, due to its association with illegal use. Cannabis (THC) has a specified blood limit of 2 micrograms/L and elevated blood levels could lead to prosecution. Although food supplements containing CBD oil may claim to be free from THC they still have the potential to contain traces of THC, even after the manufacturing process. (8)

## Interactions

Information regarding interactions is primarily based on *in-vitro* studies which describe CBD to be a potent inhibitor of CYP 1A1, CYP 1A2, CYP 1B1, CYP 2A6, CYP 2B6, CYP 2C19, CYP 2C9, CYP 2D6 and CYP 3 family. (4, 15) CBD is metabolised via hydroxylation through CYP 2C19 and 3A4 and

it is excreted by the kidneys. (4, 9) Moderate to severe impairment of kidney or liver function may theoretically reduce the clearance and/or excretion of CBD. Therefore, clinicians are advised to monitor for potential adverse effects/interactions that may occur as a result of raised serum CBD levels. Potential interactions have been reported with some medicines including anticoagulants and antiepileptic medicines. For further information on these potential interactions please see the UKMi Q&A Cannabis based medicinal products potential drug interactions, with specific reference to tables 1 and 3 of this Q&A.

The extent to which CBD may interact with other medicines is relatively unknown. Additionally the purity of individual products may differ, possibly due to undisclosed ingredients or variation in content of THC and CBD, which will have an effect on potential drug interactions. If a patient is self-administering CBD they should inform their doctor or pharmacist. Clinicians should be aware of potential interactions with medications that are metabolised by the CYP enzymes and of the use of CBD in combination with medicines that they may have additive effects. Readers may also wish to consult free resources such as the Indiana University School of Medicine Drug Interactions Flockhart Table™ for information on medicines that are affected by P450 enzymes.

CBD oil containing products have the potential to cause adverse reactions as well as interact with conventional medicines. Reporting adverse reactions via the Yellow Card Scheme can lead to important warnings about the safety of medicines. Healthcare professionals and patients can report any suspected adverse reactions to CBD oil or cannabis-based medicinal products using the Yellow Card Scheme. The easiest and quickest way to report adverse reactions is online at http://www.mhra.gov.uk/yellowcard.

## Summary

- Due to an increasing popularity of self-administration of over-the-counter bought CBD, doctors and pharmacists should be aware of its potential adverse effects and interactions.
- The most common adverse effects found in studies were somnolence, decreased appetite, vomiting, diarrhoea and elevated liver enzymes.
- Moderate to severe impairment of kidney or liver function may theoretically reduce the clearance and/or excretion of CBD.
- The data available suggests that CBD interacts with cytochrome p450 enzymes consequently, caution is recommended when CBD is co-administered with medications that are metabolised by this pathway.
- Readers should consult the UKMi Q&A Cannabis based medicinal products potential drug interactions for further information on potential drug interactions.
- Information regarding CBD safety is limited to few human studies and information should be interpreted cautiously. Further studies are needed to evaluate the full safety profile.

## Limitations

- This Q&A focuses on CBD distinct from cannabis-based medicinal products.
- This Q&A considers adverse effects and drug interactions. Information on the controlled status of CBD can be found in the 2018 Home Office Drug Licensing Factsheet- Cannabis, CBD and other cannabinoids.
- The information for this Q&A is derived from human studies only and the list of adverse effects are not exhaustive.
- Some studies used highly purified CBD whilst others used preparations containing other components (sesame seed oil, THC) which may have contributed to adverse effects/interactions.
- Patients included in these studies are characterised by poor prognosis, and have multiple co-morbidities and polypharmacy.

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## Search strategy

Please specify which of these are used if appropriate, (whether or not all of them yielded useful information) and add others if necessary:

- Embase (cannabidiol/ae, it [limit human and English language])
- Medline (cannabidiol and drug interactions [limit human and English language])
- Medline (cannabidiol/ae [limit human and English language])
- MiDatabank (cannabidiol)
- Micromedex (cannabidiol)
- Home Office
- Medicines and Healthcare products Regulatory Agency
- European Medicines Agency
- Food Standard Agency
- Royal Pharmaceutical Society
- National Institute for Health and Care Excellence
- Specialist Pharmacy Service (cannabidiol)
- Martindale (cannabidiol)
- UKMI Ecompass Discussion Group
- Natural Medicines Comprehensive Database (cannabidiol)