#  Cannabidiol oil – potential adverse effects

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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. Most 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 conditions 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](https://www.gov.uk/government/publications/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](https://www.nhs.uk/conditions/medical-cannabis/) and [NHS England website](https://www.england.nhs.uk/medicines/support-for-prescribers/cannabis-based-products-for-medicinal-use/). CBD oil is commonly referred to as hemp seed oil, although they are two distinct products. CBD oil is typically extracted from flowering buds of the cannabis plant whereas hemp seed oil is derived from cold pressing of cannabis
seeds (5, 6).

Epidyolex® is a CBD-containing medicine available only on prescription that has recently been approved for use by the National Institute for Health and Care Excellence (NICE) in conjunction with clobazam as adjunctive therapy of seizures associated with Lennox‑Gastaut syndrome or Dravet syndrome, for patients aged 2 and older (7,8). It is listed under Schedule 2 of the 2001 Regulations (9).

**Non-prescription CBD products**

In the UK CBD-containing products are also sold as food supplements and are available on the high street (10). Since these products do not fall under the 2012 Human Medicines Regulation’s definition of a medicinal product, they are not required to meet good manufacturing practice, including safety, quality and efficacy standards. Any variation in the purity of individual products (such as variation in the content of CBD or THC) could affect their potential adverse effects or drug interactions. Based on findings by the government’s Committee on Toxicity (COT), the Food Standards Agency (FSA) is advising people who are pregnant, breastfeeding or taking any medication not to consume non-prescription CBD products. Healthy adults are advised by the FSA to think carefully before taking CBD, and to keep their daily intake at, or below, 70mg (about 28 drops of 5% CBD) unless otherwise advised by a healthcare professional (11). If a patient is self-administering CBD they should inform their doctor or pharmacist and it would be prudent for anyone wishing to use a CBD-containing supplement to obtain their supply from a reputable source. The FSA is also giving the CBD industry a deadline of the 31 March 2021 to submit valid novel food authorisation applications. This process ensures novel foods meet legal standards, including on safety and content. Only products which have a valid application will remain on the market after this time.

## Answer

### Adverse effects

Safety was a focus of a meta-analysis of studies in which patients with Dravet or Lennox-Gastaut syndromes received either placebo (n=227) or an oral purified CBD solution (100mg/ml) (Epidiolex®, US trade name for Epidyolex®) as adjunctive treatment to pre-existing antiepileptic regimens (n=323) (12,13). Of the four included studies, one looked at the safety of add-on CBD in a range of doses in patients with Dravet syndrome. The other three investigated the safety and efficacy of twice daily add-on CBD in Dravet and Lennox-Gastaut syndromes. Adverse effects for which the incidence rates for CBD and placebo were found to be statistically significantly different are listed below (13) (GWPCARE1 Part A;GWPCARE1 Part B;GWPCARE3;GWPCARE4) (14-17)):

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse Effect** | **CBD (rate)** | **Placebo (rate)** | **P value** |
| Treatment-related | 55.7% | 26.9% | <0.001 |
| Serious and treatment-related | 7.7% | 0.4% |  0.003 |
| Somnolence | 24.5% | 8.4% | <0.001 |
| Decreased appetite | 20.1% | 4.8% | <0.001 |
| Diarrhoea | 18.2% | 8.6% |  0.001 |
| Increased alanine or aspartate aminotransferases > 3 times upper normal limit | 16.1% | 0.9% | <0.001 |

In these studies, 11.1% of CBD patients and 2.6% of placebo patients withdrew from treatment (any reason) (Risk Ratio 3.54, 95% CI 1.55-8.12; p=0.003). Treatment was discontinued due to adverse effects in 8.9% of patients in the CBD groups and in 1.8% of placebo patients (p=0.0002) (13).

Adverse effect incidence rates for CBD 5mg/kg, CBD 10mg/kg and CBD 20mg/kg were also considered separately versus placebo rates. There were no statistically significant differences between the rates for placebo and CBD 5mg/kg, or between placebo and CBD 10mg/kg other than for somnolence. Statistically significantly higher rates were found with CBD 20mg/kg than placebo for the effects listed in the table above, but also for sedation (p=0.042) (13).

Analysis of the three studies other than the dose-ranging study (15-17 (GWPCARE1B, 3 and 4)), found that adverse effects were most commonly seen within the first 14 days of dose escalation. Effects that occurred in more than 10% of treated patients were pyrexia, upper respiratory tract infection, somnolence, decreased appetite, diarrhoea, vomiting, nasopharyngitis, status epilepticus, fatigue, convulsion and lethargy. Reports of somnolence were more frequent in patients who were also receiving clobazam (17).

GWPCARE5 is an open-label extension study of GWPCARE1, 3 and 4 mentioned above (15-17), and of a further study in Dravet syndrome ((GWPCARE2) 19), as yet unpublished. Over 600 patients entered GWPCARE5 and received CBD treatment at a mean modal dose of 21-23 mg/kg/day for a median of 38-39 weeks. For these patients, treatment-emergent adverse effects were found to be consistent with those reported in the 14-week original studies (20, 21).

Dose-related elevations of liver transaminase enzyme levels in GWPCARE5 were reported in 10.1% of 336 patients with Lennox-Gastaut syndrome and in 17.2% of 128 patients with Dravet syndrome (20, 21). These elevations occurred most often in patients receiving valproic acid which itself is known to be hepatotoxic (20, 21). Clobazam has also been found to increase the incidence of transaminase elevations with CBD, but to a lesser extent than valproate (22, 23).In the majority of cases in GWPCARE5, transaminase elevations resolved spontaneously, after treatment discontinuation, or following CBD/concomitant antiepileptic drug dose reduction, with resolution being achieved at similar rates for each. No patient met the criteria for serious drug-induced liver injury (alanine or aspartate aminotransferases (ALT/AST) >3 times upper limit of normal (ULN) with concomitant total bilirubin >2 ULN (20, 21).

In the documentation submitted for the EU authorisation of Epidyolex, safety data from Lennox-Gastaut and Dravet syndrome randomised controlled trials (RCTs) were pooled and presented together. In the Lennox-Gastaut syndrome/Dravet syndrome pool, 456 patients were exposed to CBD (pool Dravet syndrome, n=221; pool Lennox-Gastaut syndrome, n=235) and 292 to placebo. All patients received adjunctive antiepileptic drugs. In line with the above findings, the most common adverse events reported with CBD at the recommended maintenance dose of 10mg/kg/day were somnolence (23.7%), decreased appetite (16.5%), pyrexia (17.3%), diarrhoea (12.9%) and upper respiratory tract infection (10.1%). Irritability was reported in 7.2% of patients receiving CBD 10mg/kg/day, raised ALT in 4.3%, raised AST in 3.6% and raised gamma-glutamyl transferase (GGT) in 4.3%. Most cases of ALT elevation occurred within the first 30 days of use, but some (particularly those involving concomitant valproate) occurred 6-18 months after treatment was started in clinical trials. The majority of transaminase elevations were < 3 times the ULN. However, in patients with > 3 times the ULN elevation in transaminases, there was an increased risk for a dose of 20mg/kg/day, whereas the risk for 10mg/kg/day was comparable to that of placebo. Hepatotoxicity was the main safety issue identified (23).

Human studies using CBD doses from 5 to 50mg/kg per day in epilepsy (various forms) and ulcerative colitis have identified somnolence and/or fatigue, decreased appetite, respiratory tract infections, vomiting and diarrhoea as commonly reported adverse effects with CBD (15-17, 24-26). The long-term safety of CBD is yet to be established, and further, rarer adverse effects of CBD may become apparent with increasing patient exposure (27). Other adverse effects found in studies with CBD are discussed below.

In an open-label trial of 162patients with treatment resistant epilepsy, five (3%) patients were diagnosed with mild to moderate thrombocytopenia related to CBD use, and one (1%) had severe thrombocytopenia that resolved when concomitant valproate was stopped. One patient (1%) taking valproate with CBD developed hyperammonaemia which led to CBD discontinuation (26).

Sixty patients were randomised to treatment with CBD or placebo in a double-blind trial investigating the effects of CBD in symptomatic ulcerative colitis. Most adverse effects were found to be mild or moderate in severity, but three patients on CBD 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 that 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 (24).

An open-label evaluation of CBD in dystonic movement disorders (n = 5) found hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation to be among the adverse effects of CBD, which were described as mild. In two patients with coexisting Parkinsonian features, CBD at doses over 300 mg/day exacerbated the hypokinesia and resting tremor (28).

In a small study (n=5) in which CBD was trialed for refractory seizures in Sturge-Weber syndrome, one patient reported eye exotropia and redness. The authors concluded this was possibly related to CBD (29).

There is also a published case report of acute generalised exanthematous pustulosis in a 63-year-old man who self-medicated with CBD for hypertension. The patient had a history of localised plaque psoriasis. He was treated with cefalexin and methylprednisone in hospital, advised to discontinue the CBD, and discharged with prednisone (tapering dose) and triamcinolone cream. The pustules resolved within a few weeks (30).

Finally, the SPC for Epidyolex® warns that if cannabidiol has to be discontinued, the dose should be decreased gradually. In clinical trials, cannabidiol discontinuation was achieved by reducing the dose by approximately 10% per day for 10 days. A slower or faster down titration may be required, as clinically indicated, at the discretion of the prescriber (22).

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.

Information from the trials mentioned above should be interpreted with caution as not all studies have carried out statistical analyses to confirm an association between the adverse event and the use of CBD. Moreover, most trials have used highly purified CBD whereas patients may be using a multi-constituent product, perhaps containing THC which can 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. 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. Due to its association with illegal use, the UK government has included THC under drug driving law with a threshold blood limit of 2 micrograms/L and elevated blood levels could lead to prosecution. The presence of even trace amounts of THC in CBD products may affect the individual’s clinical/psychological status and driving ability (31).

### Adverse Effects Associated with Drug Interactions

As many as 60% of adverse drug reactions are preventable and interactions with other drugs are among the possible causes (32). CBD is metabolised via hydroxylation through CYP 2C19 and 3A4 and excreted by the kidneys (4,33). It has been shown to inhibit cytochrome P450 isoenzymes. For information on potential interactions, please see the UKMi Q&A [Cannabis based medicinal products potential drug interactions](https://www.sps.nhs.uk/articles/cannabis-based-medicinal-products-potential-drug-interactions/), with specific reference to tables 1 and 3.

CBD is excreted by the kidneys and moderate to severe impairment of kidney or liver function may theoretically reduce its clearance. The SPC for Epidyolex® advises that cannabidiol is used with caution in patients with moderate or severe hepatic impairment and recommends a lower starting dose in these patients (22). Clinicians are advised to monitor for potential adverse effects/interactions that may occur as a result of raised serum CBD levels.

Healthcare professionals and patients can report any suspected adverse reactions to CBD oil or cannabis-based medicinal products using the Yellow Card Scheme. Reporting adverse reactions via the Yellow Card Scheme can lead to important medicines safety warnings. The easiest and quickest way to report adverse reactions is online at <http://www.mhra.gov.uk/yellowcard>.

## Summary

* Self-administration of over-the-counter bought CBD is increasingly popular and doctors and pharmacists should be aware of its potential adverse effects.
* The Food Standards Agency (FSA) is advising people who are pregnant, breastfeeding or taking any medication not to consume non-prescription CBD products. Healthy adults are advised by the FSA to think carefully before taking these products, and to keep their daily intake at, or below, 70mg (about 28 drops of 5% CBD) unless otherwise advised by a healthcare professional.
* Somnolence (drowsiness), decreased appetite, diarrhoea and raised serum aminotransferases (liver enzymes) were side effects significantly associated with the use of an oral purified CBD solution (100mg/ml) (Epidiolex/Epidyolex®, GW Pharmaceuticals) in a meta-analysis of studies involving 550 patients with Lennox-Gastaut or Dravet syndrome.
* Other effects found to occur very commonly in treated patients in CBD studies for Lennox-Gastaut or Dravet syndrome were vomiting, pyrexia and fatigue.
* Reports of somnolence were more frequent in patients also receiving the antiepileptic clobazam.
* Most serum aminotransferase elevations occurred in the first 30 days of treatment but some occurred up to 18 months after treatment initiation in clinical trials. This adverse effect is more likely to occur in a person who is also receiving valproate (an antiepileptic), higher doses of CBD and (to a lesser extent) clobazam.
* Theoretically, moderate to severe impairment of kidney or liver function may reduce the clearance and/or excretion of CBD which could increase the risk of side effects occurring. The SPC for Epidyolex® advises that cannabidiol is used with caution in patients with moderate or severe hepatic impairment and recommends a lower starting dose in these patients.
* Readers should consult the UKMi Q&A [Cannabis based medicinal products potential drug interactions](https://www.sps.nhs.uk/articles/cannabis-based-medicinal-products-potential-drug-interactions/) for further information on potential drug interactions.
* CBD-containing products are commonly advertised to be free from tetrahydrocannabinol (THC) but have the potential to contain traces of THC, even after the manufacturing process. THC has psychotropic properties and may contribute to potential adverse effects.
* The purity of individual products may differ, possibly due to undisclosed ingredients or variation in content of CBD (as well as THC), which will have an effect on potential adverse effects or drug interactions. Anyone wishing to use a CBD containing supplement should ensure they obtain their supply from a reputable source.
* The FSA has requested that all CBD products sold as food supplements will require a valid novel food authorisation application to be submitted by the 31 March 2021 to meet legal standards on safety and content.
* Information regarding CBD safety is limited to a 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. Information on the controlled status of CBD can be found in the 2019 [Home Office Drug Licensing Factsheet- Cannabis, CBD and other cannabinoids](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/825872/factsheet-cannabis-cbd-and-cannabinoids-2019.pdf).
* 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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## Quality Assurance

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27th February 2020

### 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)