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# OVER THE COUNTER CANNABIDIOL (CBD) PRODUCTS

*A practical guide for GPs*

*June 2021*

*primarycarecannabisnetwork.com*

# WHY IS IMPORTANT FOR GPS TO KNOW ABOUT CANNABIDIOL (CBD) ?

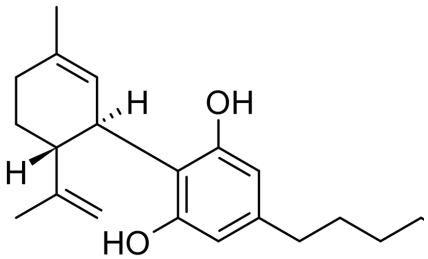
The use of over the counter CBD products has increased in line with a growing trend for people to explore more natural health and wellness solutions to common health problems. YouGov data from 2019 estimated that 11% of UK adults had tried a CBD product, with strong future growth predicted in this sector [1].

A more recent nationwide survey carried out by the PCCN in January 2021 found that patients are regularly discussing CBD in consultations with their GPs and many GPs still lack knowledge around this subject matter.

Given the prevalence of CBD use amongst the population, it is crucial that GPs are confident in having a basic understanding the properties of CBD - including therapeutic effects, dosing, side effects and potential drug interactions.

# WHAT IS CBD?

Cannabidiol is one of over 100 phytocannabinoids produced by the cannabis plant – Cannabis sativa. Phytocannabinoids are bioactive, lipophilic, bioactive molecules synthesised in glandular trichomes of the female flower of the plant.




Phytocannabinoids interact with a wide range of cellular targets and are able to modulate our own endogenous endocannabinoid system due to molecular similarities to our endocannabinoids (anandamide and 2AG) [2].

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# KEY DIFFERENCES BETWEEN HEMP DERIVED CBD, HEMP SEED OIL AND CANNABIS BASED MEDICINES ON PRESCRIPTION

Over the counter CBD is primarily extracted from the dried female flower tops of hemp– a fast growing strain of cannabis that has been selectively bred over time for its industrial properties. Hemp strains of cannabis contain low levels of Tetrahydrocannabinol (THC) and higher levels of CBD than other strains. Over the counter CBD products are permitted to contain one milligram of the controlled drug (mainly THC but also THCV and THCA) per container regardless of the size of the container and seed types must have a maximum THC content of 0.2%.

Hemp seed oil is extracted from cannabis seeds and has only trace amounts of CBD of the hemp plant. Hemp oil is similar to olive oils and vegetable oils and containscontain a rich source of nutrients including fatty acids, omega 3 and 6, vitamins and minerals.

Cannabis based medicines on prescription (often referred to as "medical cannabis") are permitted to contain varying levels of the controlled substance THC and are currently classed as schedule 2 controlled drugs with prescribing initiation restricted to specialists on the GMC register.

| VARIABLE | HEMP SEED OIL | HEMP/ CBD OILS | MEDICAL CANNABIS |
|---|---|---|---|
| PART OF PLANT EXTRACTED | Seeds | Flowers and leaves of hemp plant | Flowers and leaves of cannabis plant |
| MAIN COMPONENTS | Omega-6 and omega-3 fatty access | Mostly CBD and B-caryophyllene with other smaller quantity phytocannabinoids and terpenoids | Mostly THC with CBD and other phytocannabinoids and terpenoids |
| THC LEVELS | None | Less than 1mg per container. Seeds used must produce less than 0.2% THC | Variable - can be up to 30% dry weight. No upper limit |
| CBD LEVELS | Little to none | Up to 20% dry weight | Variable - up to 20% dry weight |
| USES | Nutritional supplements | Sold as a "novel food" in the UK as general health and wellbeing supplements | Wide range of medical uses including epilepsy and pain |

# UK REGULATIONS

In the UK, over the counter CBD products are classed as novel foods – defined as those not consumed to significant degree before the date of the 1997 EU Food Regulations, and for which pre-marketing authorisation is required [3]. Over the counter CBD products have not been through the rigorous processes that medicines are require to be put through to gain market entry by the MHRA and are not permitted to be marketed as medicines with associated medical claims [4].

Due to a largely unregulated CBD market and the various risks that this entails for consumers, the Food Standards Agency has requested that all CBD products sold as food supplements require valid novel food authorisation application [5]. This regulatory process will ensure that only products which meet legal standards on safety and content are available to consumers in the marketplace.

# LICENSED MEDICATIONS

Epidiolex is a 98%, purified CBD, schedule 5 drug licensed for use in severe, intractable epilepsy (specifically Dravet and Lennox-Gastaut Syndrome in combination with clobazam). Sativex is a schedule 4 medication licenced for spasticity in MS and composed of a 1:1 ratio of THC: CBD.

# IS CBD SAFE?

A comprehensive study by the World Health Organisation demonstrated CBD to have relatively low toxicity, that it is well tolerated across a wide dosage range with no evidence of recreational use of CBD or any public health related problems associated with the use of pure CBD [6]. A more recent literature review on the adverse effects and toxicity of CBD concluded that possible factors contributing to adverse events with CBD use include potency, route of administration concurrent licit and illicit drug use, and drug-drug interactions [7].

# WILL CBD MAKE YOU "HIGH"?

The simple answer is 'No'. Unlike THC which can produce a euphoriating and intoxicating effect, CBD is a non-psychotropic cannabinoid and will not produce any intoxicating effects. In high doses CBD may however have a sedative/ somnolence effect [7].

# INDICATED USES OF CBD

Doctors should be aware that CBD is often touted for a broad range of health benefits, yet the evidence base remains largely confined to pre-clinical studies or animal models.

CBD is however known to have a wide range of useful therapeutic modes of actions which include anticonvulsant, analgesic, anti-inflammatory, anti-anxiety, antipsychotic, neuroprotective and immunosuppressant properties [6,8].

Although has been rapid acceleration into CBD research over recent years, the strongest evidence for CBD exists for treatment-resistant epilepsies [9,10]. For most other indications, there is only pre-clinical evidence. Phase 2 and 3 clinical trials however are currently underway in diverse areas including schizophrenia, drug dependency, tumour reduction, pain conditions, and PTSD.

# CBD FULL SPECTRUM VS BROAD SPECTRUM VS ISOLATE

Full spectrum CBD products contain a full array of compounds from the cannabis plant including cannabinoids terpenes and flavonoids. These products may at times contain small traces of THC. These products benefit from the "entourage effect" - the synergistic effect from combination of different cannabinoids.

Broad spectrum products are similar to full spectrum but THC has been entirely removed. These products still likely give some of the give the entourage effect although the processing methods vary and minor cannabinoids and terpenes are lost to varying degrees. Broad spectrum products are often labelled as 'THC free'.

CBD isolate is purified CBD containing no trace of other cannabinoids, terpenes and other active compounds

# ROUTES OF ADMINISTRATION

## ORAL

Bioavailability from oral delivery has been estimated at 6% due to low water solubility and significant first-pass metabolism in the liver. Maximal plasma concentrations are usually achieved after 60–120 min and may be up to 6 hours for oral ingestion [11].

## SUBLINGUAL / TRANSMUCOSAL

Sublingual route allows direct uptake into the blood which eliminates first pass metabolism. CBD tinctures generally are created using either ethanol or vegetable glycerine as a solvent and can be directly absorbed under the tongue or on mucosal surfaces. Administration of oil from a dropper allows for a metered dose. CBD suppositories may be suitable for those who are unable to swallow CBD capsules or take CBD oils orally. CBD tampons are also being utilised to help with painful menstrual cramps.

## INTRANASAL ROUTE

Bypassing the oral route may be of benefit to patients who experience nausea, vomiting, oral mucositis or impaired gastrointestinal function.

## VAPING/ INHALATION

Vaporizing CBD in both oil or dried flower form has become a popular method of usage. CBD cartridges are heated to the point of vaporisation which results in rapid onset as cannabinoids are absorbed through the lungs into the bloodstream. Vaping results in fast onset of action and high systemic bioavailability. CBD oils are commonly mixed with a thinning agents. Consumers must be cautious concerning the safety of the products they purchase and should avoid products containing propylene glycol (PG), polyethylene glycol 400 (PEG 400), or other harmful additives.

## TOPICAL/ TRANSDERMAL

Topical application through creams and transdermal patches provides a pathway for local rather than systemic absorption of CBD. The avoidance of the first-pass metabolism effect improves drug bioavailability and can minimise the adverse effects of higher drug peak concentrations.

## SMOKING

Smoking involves direct combustion of CBD/ dried hemp flowers can produce harmful toxins which are damaging to the lungs and should be actively discouraged.

# DRUG INTERACTIONS

CBD is known to act as an inhibitor of P450 isozymes. CBD is a potent inhibitor of CYP2C19 and CYP3A4 and caution should be taken when cannabis-based medicines are co-administered with any medications that are CYP inhibitors or inducers [12].Common examples of P450 inducers include Carbamazepine, Rifampicin and Phenytoin. Common inhibitors of P450 include Sodium valproate, Ciprofloxacin, St John's Wort, Sulphonamide, Cimetidine, Omeprazole, Antifungals, Amiodarone, Isoniazid, Erythromycin, Clarithromycin.

Broad spectrum CBD products may increase the actions of warfarin and other anticoagulants leading to increased risk of bleeding and for such patients the INR should be monitored closely [12,13].

There is potential for CBD to interact with commonly prescribed anti-epileptics including clobazam but the significance of these interactions have yet to be elucidated and more work in this area is required [7,14].

# POTENTIAL ADVERSE EFFECTS

CBD formulations in clinical trials have been most commonly investigated in patients with treatment resistant epilepsy (receiving Epidiolex) and the majority of adverse events reported have been mild-moderate with the most common being somnolence, diarrhoea and vomiting and dizziness [7] . Reports of somnolence were more frequent in patients also receiving the antiepileptic clobazam [15].

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 [7] . Several epilepsy clinical trials have reported elevated aminotransferase enzyme levels with CBD administration although it is likely not CBD directly causing this effect but rather CBD in combination with other anti-epileptic drugs, in particular valproate [7, 8].

# DOSING

There is very much an individualised response to the pharmacokinetics and dosing of CBD and specific dosing regimes are beyond the scope of this guidance.

Anecdotally, most people find therapeutic response at around 100 to 200 mg CBD per day but some will need a much lower dose than this and a few a higher dose. Around 10% of sensitive individuals seem to need much smaller doses [16]. A sensible approach for most is to start at a low dose of CBD and gradually titrate up.

The current classification of over the counter CBD products as novel foods means that GPs should treat these in the same way as any other general health or food supplement and should not treat these products as medicines and avoid making any claims that these non-medical products can treat, cure or prevent disease.

# RECOMMENDED CHECKLIST FOR CONSUMERS

- Is there a batch, lot, or control number?
- Is there a production date or expiration date?
- Is there GMP certification?
- Is a robust, third-party lab testing report, which outlines cannabinoid profile including lab measured total amount of CBD available for this product?
- If it is a full-spectrum product, is there a terpene profile?
- Does the company have an independent adverse event reporting programme?
- Have products been lab tested by batch to confirm THC levels are legal and contain no pesticides, heavy metals or residual solvents?
- Are there appropriate warnings for use, including any individuals for whom the product is contraindicated, as appropriate; and instructions for use and appropriate storage?
- Is there accurate labelling which ensure that consumers understand what they are buying?
- Is the product certified organic? (organic seeds, harvested, extracted and bottled extract following a certified organic process)
- Ensure the product does not make any medical claims and is in compliance with EU food safety laws

- Ideally consumers should keep to the same one reputable product since switching brands may result in switching ingredients or quantities.
- Avoid taking multiple products containing the same or similar ingredients.
- Keep an up-to-date list of all the products and medicines (from prescribed to purchased) being taken to inform your GP and other healthcare professionals.
- Report any side effects that may be associated with the product(s) MHRA via https://yellowcard.mhra.gov.uk/.

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