

THE MEDICAL CANNABIS CLINICIANS SOCIETY

A CLINICIAN'S GUIDE TO CBD

UNDERSTANDING CANNABIDIOL



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MCS Medical Cannabis
Clinicians Society

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INTRODUCTION

THE MEDICAL CANNABIS CLINICIANS SOCIETY



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Over the past few years, over the counter Cannabidiol (CBD) products have gained popularity in the UK and across the world. We have seen unprecedented growth in the quantity and range of CBD products available for purchase on the high street and from online retailers.

CBD appears to have caught the imagination of the general public, who are using it for a number of health conditions ranging from pain and anxiety to depression and sleep. According to the Centre for Medical Cannabis, surveys conducted in 2019 by Dynata and YouGov indicates that between 8- 11% of UK adults respectively - approximately 4-6 million people - have tried CBD products.

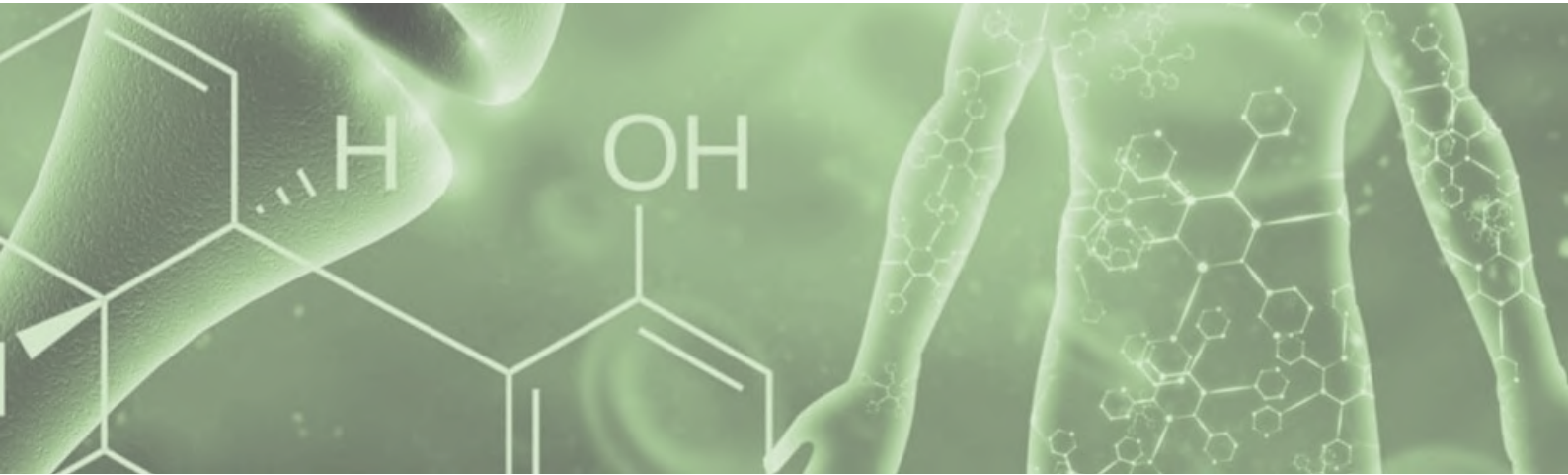
Currently, doctors report receiving mixed messages as to whether these products are legal, safe and effective and clinicians are largely unfamiliar with what patients are using. Given this widespread use of CBD, it is crucial that doctors are confident in understanding the properties of CBD and how it may affect our patients - including therapeutic effects, dosing, side effects and potential drug interactions.

This guide provides an overview of CBD for clinicians, including its modes of action and therapeutic effects, pharmacodynamics and dosing. We also summarise the current legal status of CBD in the UK.

We hope that the information contained in this publication will help doctors understand CBD and help guide their patients to the safest and most effective and evidence-based products available.

THE ENDOCANNABINOID SYSTEM

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The endocannabinoid system (ECS) is a complex cell-signalling system and is universal to all vertebrates.

The ECS consists of endocannabinoids, cannabinoid receptors, and enzymes that regulate biosynthesis and degradation of endocannabinoids.

The ECS has been implicated in a variety of disease states and important regulatory functions, including:

- Anxiety
- Appetite
- Autonomic functions
- Bladder function
- Cancer control
- Energy balance
- Female reproductive function
- GI function
- Homeostasis
- Inflammation
- Memory
- Metabolic functions
- Motor control
- Neurogenesis
- Neuroplasticity
- Neurotransmission
- Regulation of pain
- Sleep

- Social behaviour
- Stress response
- Thermoregulation

CB1 and CB2 are the two main cannabinoid receptors found within our bodies which we know most about so far, although there are likely others involved to a lesser degree.

They are both G-protein coupled receptors located on presynaptic membranes that detect molecules outside the cell and activate internal signal transduction pathways and cellular response.

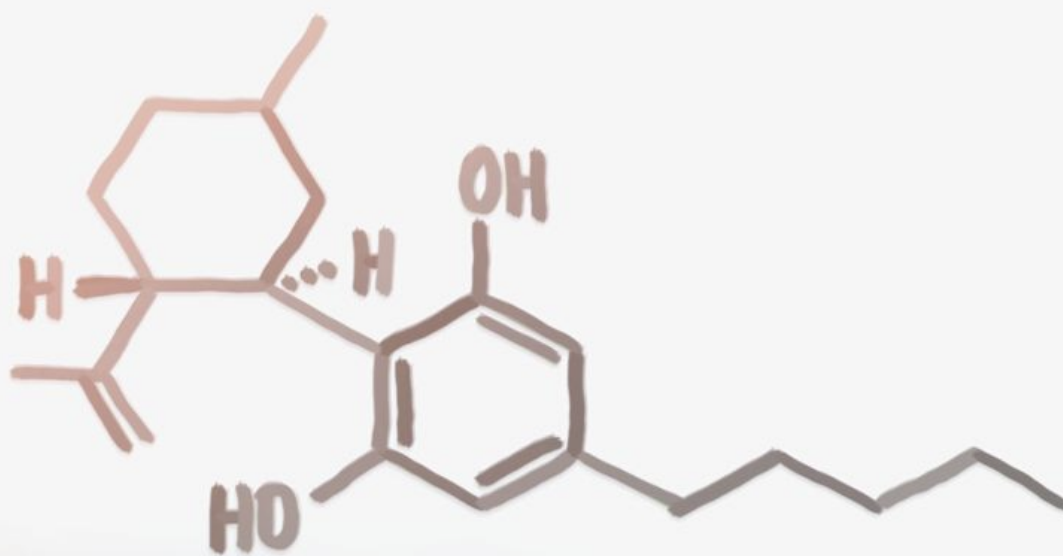
- CB1 is primarily located in the central nervous system with some expression in peripheral tissues.
- CB2 receptors are found in the periphery on cells with immune function, in the gastrointestinal tract and at low densities in the central nervous system.

Anandamide and 2-Arachidonoylglycerol (2AG) are our two main endogenous endocannabinoids, which act as neurotransmitters/ ligands binding to CB1 and CB2 receptors.

They are both synthesised on demand to maintain homeostasis.

WHAT IS CBD?

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The cannabis plant *Cannabis sativa* contains over 500 natural compounds including terpenes, flavonoids and 113 known phytocannabinoids.

Phytocannabinoids are lipophilic molecules, synthesised in the glandular trichomes of the unfertilised female cannabis flower and are able to modulate our endocannabinoid system due to molecular similarities to anandamide and 2AG.

The best-known and most widely studied of these phytocannabinoids are CBD and THC (Tetrahydrocannabinol).

CBD is a non-psychomimetic or non-psychoactive cannabinoid and is of great research interest due to its multi-modal properties in various medical conditions.

Tetrahydrocannabinol (THC) is responsible for the main psychotropic effect of cannabis.

Over the counter CBD which can be bought without a prescription is primarily extracted from the dried female flower tops of hemp or from the leaves and stems – a fast growing strain of *Cannabis sativa* that has been selectively bred over time for its industrial properties.

Hemp strains of cannabis contain substantially less THC and higher levels of CBD than other cannabis strains and the trace percentages of THC have almost zero chance of causing a psychomimetic effect.

WHAT IS CBD?

Continued

CBD OIL VS HEMP SEED OIL

CBD is sometimes confused with hemp seed oil but there are distinct differences.

Hemp oil is extracted from cannabis seeds and has only trace amounts of CBD of the hemp plant, whereas CBD is produced in glandular trichomes of female flowers and to a lesser extent from the leaves and stems.

Hemp oil is similar to olive oils and vegetable oils and contains a rich source of nutrients including fatty acids, omega 3 and 6, vitamins and minerals.

Hemp oil is widely used as an addition to cosmetics, balms and skin creams and in its refined form has a number of useful industrial applications.

CANNABIS BASED MEDICAL PRODUCTS (MEDICAL CANNABIS)

Chemovars, also known as chemotypes, refer to the breakdown of a plant species according to chemical composition.

Cannabis chemovars have been selectively bred over centuries to produce active compounds such as THC, CBD and other lesser known minor cannabinoids and terpenoids in different but much smaller concentrations and proportions.

All *Cannabis sativa* chemovars produce active compounds, but each variety produces these compounds in different concentrations and proportions.

The major difference between over-the-counter CBD oils and cannabis based medical products is that the latter can contain varying concentrations of THC, above the 0.2% trace amount allowed in OTC products.

In November 2018, cannabis-based products for medical use (CBMP) were moved from Schedule I to Schedule 2 classification of Misuse of Drug Regulations. The re-scheduling meant that CBMP could be prescribed medically by any doctor on the GMC specialist register for an unmet clinical need.

GPs can continue to prescribe CBMPs under shared care arrangements.

The Government has defined a CBMP in humans as a product which:

1. is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers);
2. is produced for medicinal use in humans; and
3. is:
 - (i) a medicinal product, or
 - (ii) a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (1).

Home Office and MHRA approvals require the content and ratio of THC/CBD to be declared, a certificate of analysis, a valid GMP certificate from the site of manufacture, a justification for special clinical need and prescription by a doctor registered on the GMC Specialist register.

All CBMP are Schedule 2 controlled drugs and are subject to the full controlled drug requirements of any other Schedule 2 drug which includes strict rules around labelling, storage and prescriptions.

WHAT IS CBD?

Continued

FULL SPECTRUM VS BROAD SPECTRUM VS ISOLATE

Full spectrum CBD products contain the full array of cannabinoids (including THC), terpenes and flavonoids.

Full spectrum CBD benefits from the entourage effect - the synergistic effect from combination of different cannabinoids.

Broad spectrum products are similar to full spectrum but THC has been removed.

These will still likely give some of the entourage effect (synergy of the various bioactive molecules), 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 so the product contains no trace of other cannabinoids, terpenes and other active compounds.

These products do not benefit from the entourage effect, but consumers can feel confident that there are no traces of THC.

This may be of particular relevance important for some professionals such as athletes and pilots where drug testing is a mandatory requirement, so offers another 'THC free' choice.

Patients and users often report that CBD isolate products don't produce as noticeable an effect vs. broad or full spectrum CBD hemp products, but there is no large human data to support this.

LICENCED CANNABIS BASED PRODUCTS

A drug company must have a product licence to advertise and sell a medicine.

Obtaining a licence for a medication is both timely and costly and involves running clinical trials for a specific illness or condition.

In the UK, the MHRA assess data from clinical trials and licences are only granted if strict safety and quality standards are met.

There are currently two licenced cannabis based medical products available in the UK - Sativex and Epidyolex.

Sativex is a schedule 4 medication licenced for spasticity in MS and is composed of a 1:1 ratio of THC to CBD.

Epidyolex is a 98% pure CBD preparation, schedule 5 drug and has been approved for the treatment of severe epilepsy in Dravet and Lennox- Gastaut syndromes.

Nabilone is a synthetic cannabinoid with antiemetic properties with a licence in the UK to treat nausea and vomiting caused by chemotherapy unresponsive to conventional antiemetics.

Is CBD safe?

An extensive report by the WHO found CBD to be generally well tolerated with a good safety profile with no evidence that CBD causes intoxication, psychotic symptoms or impairments of motor or psychomotor performance in humans. To date there is no evidence of recreational use, no effects indicative of any abuse or dependence potential of CBD or any public health issue (2).



KEY DIFFERENCES BETWEEN HEMP, CBD AND CANNABIS OILS IN THE UK

VARIABLE	HEMP SEED OILS	HEMP/CBD OILS	CANNABIS OILS
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 acids	Mostly CBD and B-caryophyllene with other smaller quantity phytocannabinoids and terpenoids	Mostly THC with some CBD and other phytocannabinoids and terpenoids
THC LEVELS	None	Less than 1 mg 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	General health and wellbeing supplement	Medical use for conditions such as epilepsy and pain

INDICATED USES OF CBD

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Doctors should be aware that CBD is often promoted for a broad range of health benefits, yet the evidence base remains at large 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 the following properties:

- anticonvulsant
- analgesic
- anti-inflammatory
- anti-anxiety
- antipsychotic
- neuroprotective
- immunosuppressive

There has been rapid acceleration into CBD research over recent years. The strongest evidence for CBD exists for treatment resistant epilepsies (3-4).

For most other indications, there is only pre-clinical evidence, while for some there is a combination of pre-clinical and limited clinical evidence.

Phase 2 and 3 clinical trials are currently underway in diverse areas including schizophrenia, drug dependency, tumour reduction, pain conditions, and PTSD (5).

IN WHAT FORMS DO PATIENTS CONSUME CBD?

A CLINICIAN'S GUIDE TO CBD



CBD is available for use in a wide variety of forms and the pharmacokinetics and pharmacodynamics of CBD and other cannabinoids vary as a function of the route of administration.

Oral

CBD is a highly lipophilic molecule with low oral bioavailability. Oral and gastrointestinal tract absorption is therefore slow, erratic and leads to variable pharmacokinetics.

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.

Oils with graduated demarcated pipettes and capsules allow for convenient and more accurate dosing in terms of the amount consumed but do not account for individual differences in likely absorption and bioavailability.

CBD products infused into food and beverages will cause the CBD to be digested and metabolized. The amounts in these products tends to vary but generally are quite low per serving.

Sublingual / transmucosal

This route of administration allows direct uptake into the blood which eliminates first pass metabolism.

CBD tinctures generally are created using either ethanol or vegetable glycerin as a solvent and can be directly absorbed under the tongue or on mucosal surfaces.

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 although the human data is lacking currently in this area.

IN WHAT FORMS DO PATIENTS CONSUME CBD?

Continued

Intranasal route

Bypassing the oral route may be of benefit to patient 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 use. CBD cartridges are heated to the point of vaporization 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. Cannabis-related effects generally begin within a few minutes of the first inhalation. Peak plasma levels after 10 mins and remain active for 3-5 hours.

CBD oils are viscous and are commonly mixed with a thinning agent to allow the cartridge to function as intended.

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 such additives as there is evidence they produce noxious compounds when they are heated past a certain temperature.

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

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.

Transdermal applications allow a steady infusion of a drug to be delivered over a prolonged period of time, while also minimising the adverse effects of higher drug peak concentrations, which can improve patient adherence.

There may be low skin penetration of drugs with a hydrophilic structure. There are many over-the-counter patch products available but many are not formulated to deliver active ingredient (CBD) transdermally and will have variable bioavailability depending on the product.

Research into cannabinoid delivery systems is growing and it is expected that recent developments in pharmacological, pharmaceutical and technological sciences will result in new therapeutic strategies.

DOSING CBD

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We must emphasise that doctors must treat over the counter CBD products in the same way as any other general health or food supplement.

Claims that these non-medical products can treat, mitigate, cure or prevent disease can result in legal consequences. Doctors should exercise extreme caution around giving advice on specific dosing for over the counter CBD products.

However, we also recognise the widespread use of CBD amongst the general public for health purposes and patients may understandably ask their doctors for their opinion or advice around efficacy, safety and interactions with other prescribed medications.

Holistic and compassionate medical care goes beyond just knowing about prescribed medications and keeping up-to-date with advances in medicine and science is a professional duty and also forms part of the GMC Good Medical Practice Guidelines.

Gaining knowledge in CBD and cannabis-based medicines are no exception, as this duty applies to all evidence-based therapies appropriate to a patient's care.

Doctors must ensure they are able to have informed conversations with patients around this subject matter. They should also explore further why CBD is being used or considered for use as this may highlight an unaddressed clinical need.

With this in mind, we have prepared a guide which continues on the next page.



DISCUSSING CBD WITH PATIENTS

- It may be useful to discuss CBD as a supplement to a diet which can help maintain general health and well being due to its wide range of physiological effects and multiple potential sites of action both centrally and peripherally within the body.
- It can be useful to explain how CBD works in a similar way to anandamide and 2AG, modulating our own endogenous endocannabinoid system and affecting a wide range of physiological functions such as mood, sleep, inflammation and pain.
- Different types of CBD products will impact dosing requirements.
- CBD products and other cannabinoids will show a typical individualised and variable drug response which will be affected by age, tolerance, body fat percentage, genetics and metabolism) – i.e. something that works well for one person may not produce the same effect for someone else.
- CBD is excreted by the kidneys and moderate to severe impairment of kidney or liver function may theoretically reduce its clearance. Patients with reduced eGFR or liver impairment may therefore be advised to take caution and start on a lower dose of CBD.
- Typical starting regime should start with slow titration.
- For CBD naïve patients we recommend a starting dose of 10mgs daily which can be built up gradually over about 4 weeks to around 60mgs and reassess. A few people are very sensitive (about 10%) hence the importance of starting at a low dose.
- Patients may need guidance on how to accurately work out mg per ml from the container.
- It may be useful for patients to keep a journal and track usage, dosage and effect.

DRUG INTERACTIONS

A CLINICIAN'S GUIDE TO CBD



There is a general lack of data on the types of drug-drug interactions that may occur between CBD and other pharmaceutical drugs in terms of published evidence of clinically significant interactions at the doses being used by consumers via over-the-counter CBD products.

Generally, at doses of CBD below 50mg or even 100mg a day, the chance of a clinically significant drug/herb interaction is probably quite low.

However, if the patient is taking certain medications such as antiepileptics, immunosuppressive agents post-transplant or cancer immunotherapy drugs or anticoagulants, it is best practice to be especially careful and to ensure that specialists involved in a patient's care and prescribing are made aware of any CBD use.

The main considerations are as follows:

CBD is known to act as an inhibitor of P450 isozymes. Patients should talk to their doctors about whether any of the medications they are taking are metabolized by the cytochrome P450 system before taking CBD.

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 (6).

Common examples of P450 inducers include Carbamazepine, Rifampicin and Phenytoin.

Common inhibitors include:

- Sodium valporate
- 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 (7).

DRUG INTERACTIONS

Continued

A rise in liver function tests and serum concentration of some anticonvulsants has been observed with Epidyolex. In a small study of 39 adults and 42 children, raised drug levels were all within therapeutic range and AST/ALT levels were significantly increased in patients concurrently prescribed valproate and CBD (8).

In another small study in children with refractory epilepsy (n13), CBD was demonstrated to increase clobazam and norclobazam concentrations (9).

POTENTIAL SIDE EFFECTS OF CBD BASED PRODUCTS

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Information regarding CBD safety is limited to a few short-term human studies and information should be interpreted cautiously. Further study is needed on larger cohorts of CBD patients, and evaluation of CBD effects following long-term exposure.

To date, CBD has been found to have relatively low toxicity and multiple small studies have demonstrated that it is well tolerated across a wide dosage range. CBD exhibits no effects indicative of any abuse or dependence potential and there is no evidence of recreational use or any public health related problems associated with the use of pure CBD (2).

In a meta-analysis of studies involving 550 patients with Lennox-Gastaut or Dravet syndrome taking Epidyolex, adverse effects associated with CBD included somnolence, decreased appetite,

diarrhoea and increased serum aminotransferases. Reports of somnolence were more frequent in patients also receiving the antiepileptic clobazam (10).

CBD differs to THC by lacking any intoxicating features. Patients may need to be reassured that CBD will not make them feel “high”.

Two of the most common adverse effects after CBD administration are somnolence and sedation but generally these are seen at high doses of hundreds of milligrams.

Other factors such as the chemovar including those high in myrcene (a terpene with potentially sedating properties), may also be involved in this response in some people based on preclinical and case report/clinical observation but no large studies exist to confirm this.

POTENTIAL SIDE EFFECTS OF CBD BASED PRODUCTS

Continued

These effects are dose-related and may be potentiated by co-administration of the anti-epileptic drugs clobazam and valproate, and other CNS depressants (including alcohol).

Patients should be advised that their ability to drive or operate machinery could be impaired while under CBD treatment.

The pharmacokinetics and toxicity of CBD in children is not well understood as in adults and therefore we do not recommend that children should be using over the CBD products

It is recommended that any significant side effects/ adverse reactions are reported via the yellow card scheme.

LEGALITIES OF CBD PRODUCTS IN THE UK

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In the UK, CBD falls into a novel food category which allows it to be purchased legally without a prescription. A novel food is defined as a type of food that does not have a significant history of consumption or is produced by a method that has not previously been used for food. Novel foods are subject to Food Standards Agency regulations.

CBD is legal to sell over the counter in the UK as long as the product meets certain criteria. It can contain very small amounts of a controlled drug (like THC) as long as:

- a) the preparation or other product is not designed for administration of the controlled drug to a human being or animal;
- b) the controlled drug in any component part is packaged in such a form, or in combination with other active or inert substances in such a manner, that it cannot be recovered by readily applicable means or in a yield which constitutes a risk to health; and

c) no one component part of the product or preparation contains more than one milligram of the controlled drug (11).

One milligram of the controlled drug (mainly THC but also THCV and THCA) is allowed per container regardless of the size of the container.

It is widely thought that the limit of THC in legal CBD products is 0.2% but this refers to the permitted seed type which must have a maximum THC content of 0.2%.

Over the counter CBD products have not been through the rigorous processes that medicines are required to be put through to gain market entry by the MHRA and as such cannot be advertised as having medicinal properties.

Advertising or promoting CBD wellness supplements products that claim to prevent, treat or cure human disease is not permitted.

LEGALITIES OF CBD PRODUCTS IN THE UK

Continued

As a result of a lack of regulatory enforcement and rapid growth in the CBD sector over the past few years, the overall safety and quality of products cannot be guaranteed.

A number of laboratory analyses of CBD products have identified concentrations of cannabinoids that differ from the amounts advertised – in some cases involving unlawfully high levels of controlled substances, other phytocannabinoids and harmful chemicals including solvents and heavy metals.

In a recently published study, 29 different CBD products available in the UK were tested. The study found that only 38% products were within 10% of the advertised CBD content. 55% of products had measurable levels of controlled substances and detectable levels of heavy metals were found in many CBD products (12).

The Foods Standards Agency (FSA) announced a deadline of 31 March 2021 for the CBD industry to submit valid novel food authorisation applications to ensure products meet legal standards on safety and content. After this time only products with a valid application will be allowed to remain on the market to be sold directly to consumers.

This application process is both expensive and time consuming and this may result in a reduced range of products available to consumers as only larger companies can afford to take the necessary regulatory steps.

The FSA has also issued further guidance recommending a daily dose of CBD as 70mg unless under medical direction, and that CBD should not be taken by pregnant women nor taken with any other medications.

The MCCA is not aware of any scientific evidence that doses above 70mg daily are unsafe.

The usual dose range for adults with anxiety and pain, for example, is 60-100mg daily. Children with epilepsy take much higher doses – up to 12mg/kg is common.

WHAT SHOULD CONSUMERS LOOK FOR IN CBD PRODUCTS?

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Due to the largely unregulated CBD market in the UK, consumers need to take extra caution on deciding about which type of CBD product to use.

With such a wide variety of products available, some people will naturally feel confused on what constitutes an effective and high quality and safe CBD product.

One of the most important considerations is ensuring the product has what is called a COA, or certificate of analysis, which should be available for any reputable supplier or brand.

This document is proof that the batch has been tested by an approved third party laboratory and contains the stated amount of CBD on the label as well as being free from contaminants, THC above trace limits, and heavy metals as well as biotoxins.

Whilst novel food authorisation will come into force on 31 March 2021 which will ensure stricter legal standards on safety and content, in the interim we recommend that consumers refer to the checklist on the next page.



CHECKLIST FOR CBD PRODUCTS

- 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 the cannabinoid profile including lab measured total amount of CBD available for this product?
- If full-spectrum product, is there a terpene profile?
- Does the company have an independent adverse events reporting programme?
- Have products been lab tested by batch to confirm THC levels are within legal limits 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?
- Does the product make any medical claims?
- Is it in compliance with EU food safety laws?

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A CLINICIAN'S GUIDE TO CBD

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THE MEDICAL CANNABIS CLINICIANS SOCIETY

INDEPENDENT, EXPERT SUPPORT FOR CLINICIANS

The Medical Cannabis Clinicians Society is an independent community of medical cannabis pioneers – the first prescribers of this treatment in the UK.

We believe that every patient who could benefit from medical cannabis should have access to it.

We provide the medical and scientific community interested in supporting patients with medical cannabis with high-quality training and expert support.

Membership is open to those with a professional interest in medical cannabis, including clinicians, nurses, GPs, allied health professionals (AHPs), medical students, healthcare scientists, pharmacists and those working across acute, primary and community healthcare.

As part of the UK's leading group of medical cannabis experts, members have access to information to inform treatment decisions, up-to-date product guidance and support to ensure clinicians can become as confident in prescribing medical cannabis as they are with first line treatments.

With the most respected medical cannabis clinicians in the country providing support, members are better able to help their patients.

Annual membership is £90 for consultants, GPs and others and £45 for nurses and AHPs. Membership is free for medical students and we welcome international members.

Join online at www.ukmccs.org.

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