MIGHTY GREEN

The Practitioner's Guide To CBD

A fully referenced resource for Practitioners on
CBD & the **Endocannabinoid System**

Contents

Introduction

Welcome to the Mighty Green Practitioner's Guide to CBD. We have created this book for health practitioners, by health practitioners. Our aim is to give you clarity, insight and confidence in this emerging field.

The dramatic rise of CBD has been fuelled by consumer interest, with many health practitioners struggling to find credible information. According to a recent YouGov Survey commissioned by the CMC (the Centre for Medical Cannabis) in June 2019:

- Approximately 6 million adults have used CBD in the UK.
- 11% of the population had consumed a CBD product in the last year.
- Usage was higher on average among females (13%) than males (9%).

As fellow practitioners, we share your curiosity for possible mechanisms of action. In this eBook we take a deep dive into: what CBD is, the endocannabinoid system, research, clinical trials, pharmacology, legalities, and dosing.

We want to emphasise that we do not make medical claims about CBD. We are simply reporting on the scientific literature. You'll always find references from scientific papers.

Thank you for joining the Mighty Green Practitioner Benefits. Look out for our newsletters brimming with the latest CBD research. We look forward to supporting you along the way.

Wishing you the best of health

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Chapter 1: What Is CBD?

CBD is one of a family of unique molecules that naturally occur within the plant genus Cannabis. Cannabis has a number of species that fall under it; Cannabis Sativa L., Cannabis Indica and Cannabis Ruderalis.

Molecules like CBD are called cannabinoids, each with their own unique properties. There are over 100 cannabinoids that exist in Cannabis it just so happens that CBD is one that is particularly useful, safe and accessible.

Where Does It Come From?

Although CBD can come from Cannabis Indica and Cannabis Ruderalis, most is obtained from Cannabis Sativa L. This is mostly because Cannabis Indica contains high amounts of THC, the psychoactive and illegal cannabinoid. Cannabis Ruderalis is generally lesser known, and is not typically used for CBD extraction.

Cannabis Sativa L. can be split into two different types: Hemp & Marijuana. These terms are the unscientific, non-botanical terms for differentiating plants that have low vs high amounts of THC.

Hemp is the legal variety of Cannabis sativa L, because it contains below the UK legal limit of THC (less than 0.2%) in addition to CBD.

Marijuana is the illegal variety of Cannabis sativa L, because it contains high amounts of THC (0.2 - 30%) in addition to CBD.

CBD, along with other cannabinoids like CBN (Cannabinol), CBC (Cannabichromine), CBG (Cannabigerol) can also be found in Cannabis Sativa L. plants.

Concentrations of these cannabinoids vary across different subspecies of plants within the Cannabis sativa L. species.

The psychoactive cannabinoid THC is found in high concentrations in the subspecies broadly referred to as Cannabis. THC produces the characteristic Cannabis 'high' and is therefore why this subspecies of Cannabis Sativa L. is illegal.

The other subspecies is known as Hemp, which naturally contains very low levels of THC, in proportion to other cannabinoids like CBD. Mighty Green sources all our CBD products from Hemp.

How Is It Sourced?

Hemp is the preferred way to source CBD, because of the naturally low levels of THC it contains. The levels of THC found in Hemp do not typically surpass the legal limit of 0.2% set by EU and UK legislation. This makes it easy to obtain CBD without breaking the law.

Hemp also contains a host of other beneficial compounds besides just cannabinoids. Fatty acids, terpenes, flavonoids, vitamins and minerals can also be found in Hemp, which also contributes to the plant's beneficial qualities.

The whole spread of beneficial compounds can be extracted from Hemp into what is called a **full** or **broad-spectrum extract**. Conserving the mix of compounds in a broad-spectrum extract preserves the beneficial qualities of the Hemp plant.

Its desirable to extract the broad spectrum of cannabinoids, terpenes, flavonoids, fatty acids, vitamins and minerals because there is synergy between them. This is known as the **entourage effect**, whereby the whole is greater than the sum of its parts.

The full spectrum of Hemp compounds can be obtained in a few ways::

1. The most commonly used and gold standard method is by supercritical Co2 extraction. This involves passing Co2 at high pressures through a cylinder containing ground Hemp flowers to yield a viscous and dark paste. This method provides a high quality, pure extract free of residual solvent.

2. Ethanol extraction is less common but still produces a high-quality paste. Additional steps have to be taken to ensure the residual ethanol is evaporated in order to obtain a high purity extract.

3. Fractional distillation can be applied to both a Co2 and ethanol extraction, to further purify extracts to ensure compliance with THC limits, and to maximise CBD concentrations. This method also removes any lipids, waxes and chlorophyll to provide a greater taste.

History

CBD has come a long way since its first documented cases of use. Today CBD is found in the form of various extracts. But back in the day, CBD was still an undiscovered constituent of whole plants.

Although there are other constituents that provide Cannabis Sativa L with its suggested therapeutic value, CBD certainly plays a role, and has done for thousands of years.

The use of Cannabis Sativa L. as a medicine stretches both far back and wide. One of the first mentions of its use was in ancient Egypt in 2350 B.C., where it was used for diarrhoea, and as an antibiotic (Russo, 2007).

It was also mentioned in India as early as 1500 B.C., where it was used as part of Ayurvedic medicine for diarrhoea, cough, nervousness and impotence (Russo, 2005). There are also documented cases of its use in China, Africa, the Middle East and Europe ranging from 10,000 B.C. to 1890 (Russo, 2007).

In 1942, CBD was fully isolated from the plant by an American chemist called Roger Adams. It wasn't until 1980 that Dr Raphael Mechoulam studied the biological activity of cannabinoids and CBD, where it started to become apparent which ones did what (Mechoulam and Carlini, 1978).

The work of Dr Mechoulam opened the door to discover further biological mechanisms by which CBD and other cannabinoids exert their effects.

It was later realised that CBD, THC and other cannabinoids interact with specific receptors within the body. In 1988 the endocannabinoid system was discovered in the brain of rats, by identifying specific cannabinoid receptors (Devane et al., 1988). These were later found in humans.

Today, many other constituents of the endocannabinoid system have been identified, including other specific cannabinoid receptors.

How Does it Work?

CBD is known as a pleiotropic molecule. This means it produces multiple biological effects within the body all at once.

The ubiquitous effects of CBD are achieved through the interaction with many different receptors in the body, which allows it to have a diverse impact on human physiology.

Check out the Mechanisms and Pharmacology of CBD in Chapter 3 to learn more.

Arguably one of the most significant interactions CBD has is with the Endocannabinoid System (ECS).

The ECS is a core homeostatic regulator of human physiology. In laymen's terms, the ECS is like a thermostat which can turn biological activity up or down across many functional systems within the body.

Learn more about the ECS in **Chapter 2**.

Environmental stressors that pervade life in the 21st century can cause imbalance in ECS function:

- Stress
- Sleep deprivation
- Poor diet
- Sedentary lifestyle
- Infection

Cannabinoids like CBD have been suggested to support the homeostatic functions of the ECS, suggesting that they may be powerful modulators of human health.

In this way, if the ECS becomes imbalanced, cannabinoids may act to restore equilibrium within the system to prevent ill health.

Research has revealed imbalances in ECS activity across a host of chronic diseases, suggesting a role for the ECS in the development of disease (Toczek and Malinowska, 2018).

Learn more in **Chapter 4**: Research and Clinical Trials.

How To Consume CBD

CBD can be enjoyed in many different ways. It is a fat-soluble compound that is traditionally prepared with a carrier oil, which can be ingested:

- As oil droplets
- As capsules
- As edible foods
- As beverages

Alternatively, CBD can be used topically when applied to the skin:

- Lotions
- Creams
- Balms

CBD can also be transformed into a water-soluble formulation and incorporated into water-based drinks.

After the removal of waxes, fatty acids and chlorophyll, CBD can be vaporised in the form of a concentrate.

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Chapter 2: The Endocannabinoid System (ECS)

What Is The ECS?

The word cannabinoid refers to hundreds of tiny compounds that are found within a species of plant called Cannabis Sativa L. These cannabinoids also occur naturally within every single one of us. The only difference is that they are produced within us or endogenously, hence the name endocannabinoid.

The ECS as a whole is made up of three components:

1. Endocannabinoids: messengers that communicate far and wide throughout the body
2. Metabolic enzymes: they make and destroy endocannabinoids
3. Cannabinoid receptors: these bind endocannabinoids, and pass on their messages

Before the discovery of the endocannabinoid system, researchers were scratching their heads as to how cannabis was able to produce its effects. In 1988, researchers discovered the first cannabinoid receptor in the brain of rats. They found it was able to recognise the cannabinoids found within cannabis.

This sparked a search for endogenous compounds that also hit this cannabinoid receptor - the endocannabinoids. From this, the ECS as a whole was identified, and it is still being understood today.

The ECS Lowdown

The ECS exists ubiquitously in the human body to maintain homeostasis. Homeostasis is a process by which the body's internal environment is kept in continual equilibrium, despite changes in the external environment.

Think of blood pressure, fluid/electrolyte balance, body temperature - all of these need to be maintained in a sweet spot. This not only ensures optimal functioning, but also ensures against the development of disease in the body.

The ECS is the master regulator of most other bodily processes. It is like the conductor of an orchestra - it makes sure all the bodily systems are playing in harmony.

It functions in much the same way a thermostat would, turning biological activity up or down to meet the demands in response to the external environment. For example, if you start running, the ECS ensures blood vessels dilate, respiratory rate increases, and core body temperature is

maintained through sweating. On the flip side, things like digestive activity will be turned down.

The ECS acts in a very targeted way, so that it only affects biological activity that needs to be balanced at that time. For example, the ECS reduces excessive inflammation without altering digestive activity.

The activity of the ECS is tightly regulated to ensure a precise balance. Activity is controlled by metabolic enzymes which produce and degrade the messengers of the ECS, the endocannabinoids. These enzymes ensure the endocannabinoids don't hang around too long to overshoot balance once it has been achieved.

Two of the major roles of the ECS involves nervous and immune system functions. The nervous system is regulated by the CB1 receptor, which is found on neurones across different neurotransmitter systems.

This means the ECS has the ability to regulate the activity of the neurotransmitter systems, which together instruct diverse changes in human physiology (motor function, mood, sleep, eating etc.).

The immune system is principally regulated by the CB2 receptor. CB2 influences how immune cells communicate, and ultimately the levels of inflammation in the body. Inflammation is a big player in influencing human health and disease, so the ECS has an important role to play here.

Components of the ECS

Endocannabinoids

Endocannabinoids are our own naturally produced cannabinoids. They act as messengers to maintain homeostasis by activating cannabinoid receptors on cells, in the same way a key fits into a lock.

Endocannabinoids are made in one cell, and act on cannabinoid receptors on a nearby cell. This negative feedback mechanism allows endocannabinoids to override other signals acting on a cell, to make sure biological functions stay within their sweet spot.

For example, after burning a finger on a hot stove, the immune system increases inflammation. Once enough protective inflammation has been achieved, the ECS slowly reduces inflammation to avoid it becoming harmful.

Endocannabinoids are produced from the fatty acids we obtain in our diet. The omega-6 fatty acid Arachidonic Acid is used to make the two main endocannabinoids:

- Anandamide (AEA)
- 2-Arachadonylglycerol (2-AG)

Metabolic Enzymes

Both AEA and 2-AG have their own specific set of biosynthetic and degradative enzymes. This allows their respective levels to be tightly regulated for precision communication.

They are rapidly made on demand from Arachidonic Acid, that is stored in cell membranes. They are also broken down quickly. This ensures a highly sensitive communication system that can be easily turned up or down to meet dynamic demands.

These sensitive enzymes allow endocannabinoids to have a transient and localised effect. Unlike neurotransmitters and hormones, they are not stored and don't hang around for long. In this way, the ECS can regulate very specific biological processes without affecting others.

Cannabinoid Receptors

These are G-Protein coupled receptors which specifically recognise both AEA and 2-AG. Cannabinoid receptors are found on the surface of many different types of cells throughout the body.

There are two principal cannabinoid receptors:

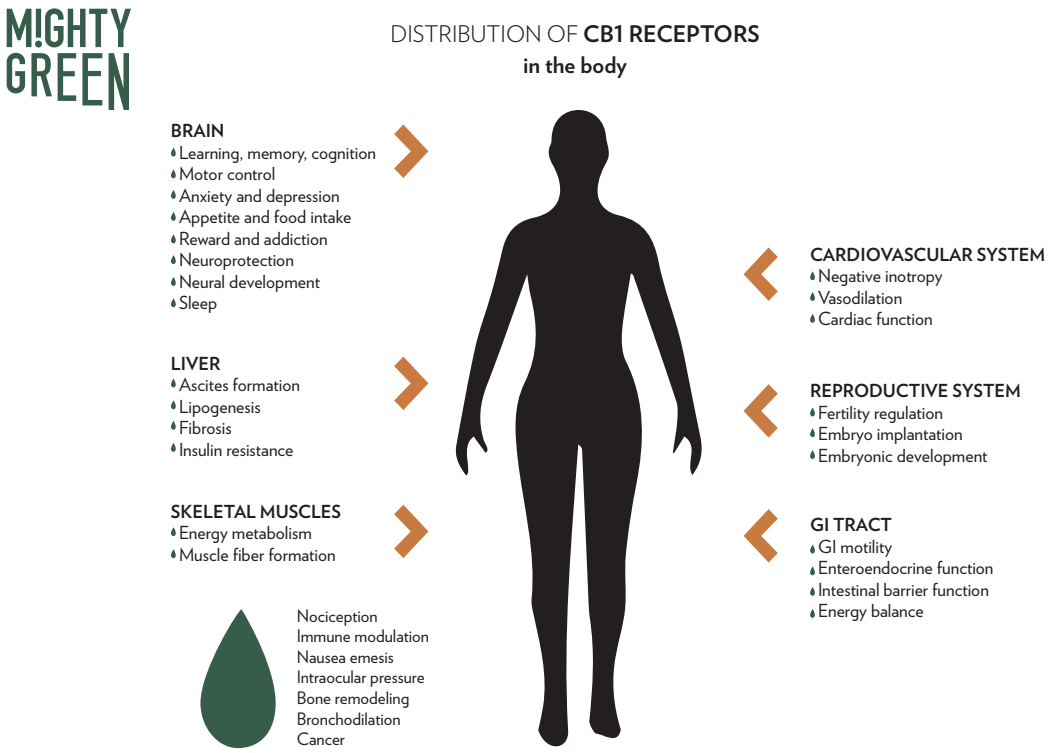
- Cannabinoid Receptor 1 (CB1)
- Cannabinoid receptor 2 (CB2)

Cannabinoid receptors bind with endocannabinoids in much the same way a key fits into a lock. Upon binding, a cascade of changes occurs to alter cellular activity, which corresponds to changes in biological processes such as:

- Appetite
- Sleep
- Mood & Emotion
- Memory
- Cognition
- Energy metabolism
- Thermoregulation
- Digestion
- PH Balance
- Blood Pressure
- Pleasure & Reward
- Pain
- Reproduction
- Inflammation
- Immune function

CB1

CB1 is the most abundant receptor in the mammalian brain (Pacher, 2013) It is densely populated in the hippocampus, amygdala, and hypothalamus. It is found to a lesser extent in other brain regions, the central and peripheral nervous system, and immune system.



CB1 is also found on organs, such as:

- Liver
- Fat tissue
- Pancreas
- Muscle
- Gastrointestinal system
- Lungs
- Reproductive organs

CB2

CB2 is mainly found in the periphery of the body, mostly on cells of the immune system:

- Macrophages
- Neutrophils
- Monocytes

- B-lymphocytes
- T-lymphocytes
- Microglial cells

CB2 can also be found to a lesser extent within the central and peripheral nervous system, bone metabolising cells - osteoclasts and osteoblasts, skin nerves and keratinocytes, the liver and pancreas.

The ECS in Health & Disease

The expression of cannabinoid receptors, activity of enzymes, and the concentration of endocannabinoids in the body can all be highly variable. Everyone has a different ECS activity based on their genetics, how they live their lives and their environments.

There are several factors which can upset the way the ECS works. Modern life - one that is especially far removed from how humans used to live can be stressful for the ECS and challenge its ability to maintain homeostasis.

These include:

- Stress
- Sleep deprivation
- Poor diet
- Sedentary lifestyle
- Infection

In certain cases, peoples ECS can become dysregulated due to how their genetics, lifestyle and environment are interacting. The ECS can become both over and under active, which upsets the balance of homeostasis in different ways.

An under active ECS, or clinical endocannabinoid deficiency (CECD) may exist in these conditions (Russo, 2016, Hill et al., 2018, Toczek and Malinowska, 2018):

- IBS
- Migraine
- Fibromyalgia
- PTSD
- Mood disorders
- Alzheimer's

On the opposite side, an overactive ECS may play a role in the following conditions (Toczek and Malinowska, 2018):

- Arthritis
- Multiple sclerosis
- Parkinsons
- Stroke
- Schizophrenia
- Alcoholism
- Anorexia

- Ulcerative colitis
- Liver cirrhosis
- Pancreatitis
- Hypertension
- Myocardial Infarction
- Obesity
- Cancer

The emergence of medical conditions often requires more than just one bodily system to become imbalanced. Take IBS for example; as well as digestive issues there are often problems with sleep, mood and fatigue. That means the immune, digestive, nervous and endocrine systems may not be working properly.

It makes sense to hypothesise then, that if all these systems are imbalanced at once, that may have something to do with the ECS, since it is the master regulator of bodily systems.

The ECS & Cannabinoids

Cannabinoids are analogous compounds to endocannabinoids. They are similar keys that fit the same locks, and can perform some of the roles that endocannabinoids can in the body; ensuring balance across the bodily systems.

This may have something to do with the tidal wave of interest in plant cannabinoids such as CBD. People are using it for all sorts of ailments, from pain to Parkinsons. It might be that cannabinoids like CBD could help support the function of an ECS that is struggling to maintain homeostasis in certain medical conditions.

It makes sense if you look at what roles the ECS has, and the fact that cannabinoids push many of the same button that endocannabinoids do.

Cannabinoids are being studied across a myriad of conditions, and may have far reaching applications for human health. In countries where cannabis is legal, the psychoactive cannabinoid THC is also of interest.

Conditions of interest include:

- Anxiety
- Pain
- Insomnia
- Neurological conditions like Parkinsons
- Neuropsychiatric conditions like Schizophrenia
- Autoimmune conditions like IBD
- Inflammatory conditions

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Chapter 3: CBD Research & Mechanisms

Here at **Mighty Green** we want to emphasise that we do not make medical claims when it comes to CBD. We are simply reporting on what the scientific literature says. You'll always find references from scientific papers.

This chapter is going to take a deep dive into clinical research with CBD, and the efficacy of its use in context of the conditions it has been studied with. There are a lot of (scientifically) unsubstantiated claims surrounding CBD. The aim of this chapter is to provide clarity around what it may or may not be efficacious for. Dosing, duration and other considerations will be included.

Before we dive into the research, it's important to point out that most CBD available for your clients will be CBD rich, whole plant cannabinoid extracts. However, most research is conducted with 99% pure, (isolate) pharmaceutical grade CBD.

The efficacy, dosing and effects can be significantly different between the two, so it's worth bearing in mind when interpreting the research. Please also refer to our Dosing Guidelines in **Chapter 5**.

An Israeli study found that pure CBD showed an inverted U-shaped dose response curve, meaning it has a very narrow therapeutic window. In contrast, they found the therapeutic effect of full spectrum CBD increased in line with increasing doses. Additionally, smaller amounts of full spectrum CBD (10 mg/kg CBD) were needed to relieve pain, whereas larger amounts of purified CBD (25 mg/kg CBD) were required to produce the same relief (Gallily, Yekhtin and Ondřej Hanuš, 2015).

A meta-analysis in patents using CBD for epilepsy found that 71% of patients using full spectrum CBD had improvements in seizure frequency, whereas only 46% of patients using isolate had improvements.

Those using full spectrum CBD reported using lower doses (6.0 mg/kg/day) than patients using purified CBD (25.3 mg/kg/day). Significantly more users of purified CBD reported mild side effects (76% vs. 33%) and severe side effects (26% vs. 7%) than those using full spectrum CBD (Pamplona, da Silva and Coan, 2018).

Indeed, the difference in clinical outcomes and dosing requirements is likely an effect of the synergy between CBD, other cannabinoids and terpenes present in full spectrum extracts. This is known as the **entourage effect**.

Epilepsy

In an open-label prospective study, 20 - 30 mg/kg/day in 72 children and 60 adults with treatment resistant epilepsy reduced bi-monthly seizure frequency (144.4 > 46.7) and seizure severity (80.7 > 34.6) after 48 weeks (Szaflarski et al., 201).

A double blind RCT in 15 patients with generalised epilepsy showed 2-300mg CBD / day for 4.5 months completely eliminated convulsions in 4 patients and partially eliminated them in 3 patients taking CBD, compared to no improvement in 7 patients in the placebo group (Cunha et al., 1980).

In a double blind RCT, 225 patients with Lennox-Gastaut syndrome (2-55 yrs) receiving 20mg/kg CBD /day for 14 weeks had 41.9% reduction in seizure frequency; those receiving 10mg/kg CBD/ day had 37.2% reduction compared to only 17.2% in the placebo group (Devinsky et al., 2018).

Another double blind RCT in 171 patients with drop seizures found 20mg/kg CBD / day for 14 weeks significantly reduced monthly seizure frequency compared to placebo (43•9% vs 21•8%). (Thiele et al., 2018)

Suggested Mechanism(s) of Action

1. Anticonvulsant mechanism of CBD may involve modulation of Ca2+ homeostasis (Ligresti, De Petrocellis and Marzo, 2016)
2. CBD might inhibit seizures in the CNS via action on GABA (Ligresti, De Petrocellis and Marzo, 2016)
3. Activation of TRPV1 and TRPV2 by CBD in the hippocampus may reduce neuronal hyperactivity in epilepsy (Ligresti, De Petrocellis and Marzo, 2016)
4. Blocking GPR55 and ENT with CBD may contribute to reduced seizures (Devinsky et al., 2014)
5. Activation of 5-HT1A receptor, alpha3 and alpha1 glycine receptors by CBD may mediate anti-epileptic effects (Devinsky et al., 2014)

Insomnia & Sleep

In a large retrospective case series at a psychiatric clinic, 25 psychiatric patients with sleep disorders taking 25 - 75mg CBD /day improved subjective sleep scores by 28% after 3 months (Shannon et al., 2019). However, in the 47 other psychiatric patients without overt sleep disorders the same doses had less of an impact. This suggests CBD's efficacy depends upon the existence of a sleep disorder.

Consistently, a double blind RCT giving 160mg CBD to 15 insomniacs improved sleep duration (> 7 hrs), reduced waking and improved subjective sleep quality compared to placebo (CARLINI and CUNHA, 1981). Lower doses of 40 & 80mg did not have this effect. CBD also had no effect on the time it takes to get to sleep.

4 Parkinsons patients with REM sleep disorder were treated with 75 - 300mg / day CBD for 6 weeks. 3/4 patients completely eliminated frequency symptoms (1-7 x per week > 0 x per week). 1 Patient still experienced symptoms (1 x / week), but still improved from 4 x / week (Chagas et al., 2014).

18-24mg CBD reduced insomnia and PTSD symptoms in a case report (Shannon and Opila-Lehman, 2015).

Suggested Mechanism(s) of Action

- CBD efficiently stops anxiety-induced REM sleep suppression (Pisanti et al., 2017a)
- High doses of CBD increases total sleep time and slow wave sleep (SWS) in rats (Hortes Chagas, Zuardi and Paulo Machado-de-Sousa, 2013)
- High doses of CBD also increased REM sleep (Babson, Sottile and Morabito, 2017), which may improve sleep quality
- Low doses of CBD decrease REM and non-REM (NREM) sleep (Murillo-Rodríguez, 2008)

Neuropsychiatric Conditions

An open label pragmatic trial found that 200 mg CBD / day for 10 weeks in 18 regular cannabis users significantly increased the volume of hippocampal substructures (+ 1.58%) compared to baseline (Beale et al.,2018). This may be of significance for conditions associated with hippocampal atrophy, including schizophrenia, Alzheimer's disease, and major depressive disorder. Control groups are needed to explore this further.

Anxiety

In a double-blind experiment, 40 healthy volunteers received either 300mg CBD, diazepam, ipsapirone or placebo. CBD significantly reduced scores of anxiety after, but not during a simulated public speaking test compared to placebo and diazepam (Zuardi et al., 1993).

However taking higher doses (600mg CBD) for Social Anxiety Disorder (n=24) before a simulated public speaking test significantly reduced scores of anxiety, discomfort and cognitive impairment during the test compared to placebo (Bergamaschi et al., 2011).

In contrast, an RCT in 57 healthy men using escalating doses of CBD (150mg, 300mg & 600mg) found that only 300mg CBD significantly reduced anxiety compared to placebo. This suggests an inverted U dose-response curve whereby an intermediate sweet spot must be hit for CBD to be effective for anxiety (Linares et al.,2019).

Most studies have used subjective reports to quantify an improvement in anxiety, without physiological markers for support. However, a preliminary report using neuroimaging in patients with Social Anxiety Disorder found that 400mg CBD significantly decreased anxiety, and altered Endocannabinoid uptake in limbic and paralimbic brain areas compared to placebo (Crippa et al., 2011).

Additionally, the anxiolytic effects of CBD may be related to its effects on cortisol secretion, whereby 300mg had a significant impact on blood cortisol levels compared to placebo (Zuardi et al., 1993).

Schizophrenia

In a randomised controlled trial, 88 patients given 1000mg CBD/day had improved psychotic symptoms and were not as severely unwell as those receiving placebo after 6 weeks (McGuire et al., 2018).

In another RCT, 800mg CBD/day for 4 weeks was similarly effective as the antipsychotic medication amisulpride. It also had significantly less side effects, notably motor disturbances, weight gain and sexual dysfunction. Anandamide was significantly higher in the serum of those receiving CBD, suggesting antipsychotic effects are related to Endocannabinoid reuptake (Leweke et al., 2012).

1250mg / day CBD for 36 days had little effect 3 patients with treatment resistant schizophrenia, although one patient experienced moderate improvements in symptom scores (Zuardi et al., 2006).

Selective attention was not improved with acute doses of 300mg or 600mg CBD compared to placebo in 28 schizophrenic patients (Hallack et al., 2010). This may be related to the acute nature of the study, as improvements in cognition have been found with CBD after 6 weeks, albeit insignificant (McGuire et al., 2018).

In contrast, despite improvements in psychotic symptoms, 600mg CBD for 6 weeks in 36 patients had no significant effect on cognitive impairments compared to placebo (Boggs et al., 2018). This may have been related to sample size.

Psychosis

In an RCT measuring brain activity, a single dose of CBD (600mg) increased activation in the parahippocampal gyrus/midbrain compared to placebo in 33 patients at high risk for psychosis. CBD increased Para hippocampal gyrus/midbrain activation towards the level seen in the control group of healthy volunteers (Bhattacharyya et al.,2018).

A single dose of 600mg CBD was also found to increase connectivity between the putamen and the prefrontal cortex in the brain of 16 heathy men (Grimm et al., 2017). Although the clinical and behavioural implications of this are not yet clear, CBD may benefit decreases in connectivity associated with psychosis.

Bi-polar Disorder

A case series of 2 patients reported 600-1200mg CBD for up to 30 days to have no effect on manic episodes. RCT's are needed to explore CBD in bi-polar disorder further (Zuardi et al.,2010).

Suggested Mechanism(s) of Action

- CBD reduces Anandamide re-uptake, partially restoring regulation of the nervous system via increased CB1 activation (Ligresti, De Petrocellis and Marzo, 2016).
- CBD activates 5HT1A to regulate serotonin signalling, which may reduce anxiety (Ligresti, De Petrocellis and Marzo, 2016).
- CBD may reduce HPA axis hyperactivity, via modulation of cortisol secretion (Zuardi et al., 1993)

Neurological Disorders

Parkinsons

CBD in a flexible dose (started with an oral dose of 150 mg/day) for 4 weeks significantly decreased psychotic symptoms and ratings of Parkinsons Disease severity in 6 patients, and was well tolerated. The only caveat here is a lack of control group (Zuardi et al., 2009).

However, an RCT found 300mg CBD for 6 weeks to significantly improve quality of life scores compared to placebo in 21 patients despite no differences in plasma BDNF and general symptom scores (Chagas et al., 2014)

Huntingtons

In a double blind crossover study, 10 mg/kg CBD/day for 6 weeks had no significant or clinically important effects in 15 Huntingtons patients (Consroe et al., 1991). Although, additional trials with larger sample sizes are needed to clarify a lack of effect.

Incremental doses of CBD (100 to 600 mg/day) over 6 weeks improved dystonia by 20-50% in a dose-related manor in 5 patients (Consroe, Sandyk and Snider, 1986). Despite antidystonic effects in 3 patients, CBD aggravated hypokinesia and resting tremor in 2 Parkinsons patients.

Multiple Sclerosis

A preliminary controlled trial in 24 patients found that a sublingual spray, which delivered 2.5mg CBD rich whole plant extract, with maximum dose of up to 120mg/day significantly reduced pain and ratings of spasticity severity compared to placebo. However, there was little difference for ratings of quality of life and general well-being compared to placebo (Wade et al., 2003).

Suggested Mechanism(s) of Action

- CBD inhibits IL-1β, IL-6, and interferon-β (IFN-β) in LPS-stimulated murine microglial cells (Pisanti et al., 2017b)
- CBD reduces adenosine uptake, which may reduce inflammation via increased A2A receptor activation (Pisanti et al., 2017b)
- CBD up-regulated glutathione transcription in microglial cells (Pisanti et al., 2017b)
- Multiple sclerosis induction in mice CBD significantly increased P13, AKT and mTOR phosphorylation in spinal cord tissue after MS reduced phosphorylation, and cytokines IFN-y and IL-17 were significantly reduced by CBD (Giacoppo et al., 2017). This may prevent apoptosis.
- CBD reduces blood brain barrier permeability via PPARγ and 5-HT1A receptors (Hind, England and O'Sullivan, 2016).
- CBD up-regulates mRNA levels for Cu–Zn superoxide dismutase, which may combat oxidative stress (Pisanti et al., 2017b)
- CBD restores Ca+ homeostasis, which may protect against Ca+ mediated neuronal apoptosis (Ryan et al., 2009)
- CBD protects against iron accumulation, which may improve mitochondrial dynamics and inhibit synaptic loss and apoptotic cell death (Da Sillva et al., 2014)
- CBD that decreases the production of TNF-α and other cytokines and COX-2 expression

(Pisanti et al., 2017a)

- CBD suppresses microglial activity and T- cell proliferation, by reducing expression of VCAM-1, chemokines (CCL2 and CCL5) and IL-1β (Pisanti et al., 2017a)

Cardiovascular Disease

In a crossover RCT, a single dose of CBD at 600mg reduced blood pressure (–5 mmHg), increased heart rate (+10 bpm) and decreased stroke volume (–13 ml) in response to physiological and psychological stressors (Jadoon et al., 2016).

Suggested Mechanism(s) of Action

- CBD causes endothelium-dependent vasorelaxation in human mesenteric arteries via CB1 receptor and/or via increasing endocannabinoid availability (Pisanti et al., 2017a)
- CBD mediates vasorelaxation in rat aortae via PPAR-γ (Pisanti et al., 2017a)
- CBD includes the release of vasorelaxant mediators like nitric oxide (Pisanti et al., 2017a)
- CBD increases vasorelaxation via increased release of COX1 and COX2 derived vasodilator products (Pisanti et al., 2017a)
- CBD increases vasodilation through reductions in ROS via increased superoxide dismutase activity (Pisanti et al., 2017a)
- CBD was found to significantly reduce apoptotic markers p38 MAPK and caspase-3, and increase AKT phosphorylation in myocytes, indicating potential for cell survival (Rajesh et al., 2010).
- CBD also reduces NF-KB and inflammation, via inhibiting ROS and nitrogen species generation (Pisanti et al., 2017a)

Inflammatory Bowel Disease

Crohns

A randomised controlled trial failed to show any improvements in Crohn's disease activity index relative to placebo with 20mg CBD / day. after 8 weeks. There were also no differences in inflammatory markers. This study only featured 19 participants, and the dose is significantly lower than that of other studies (Naftali et al., 2017).

Ulcerative Colitis

An RCT found that 500mg CBD / day for 10 weeks significantly improved Mayo scores (of remission), in addition to patient reported quality of life measures. However, more trials are needed, especially those examining inflammatory biomarkers (Irving et al., 2018).

Suggested Mechanism(s) of Action

- PPAR-γ mediated decrease in TNF-α in human intestinal cells (Pisanti et al., 2017a))
- Reduced mast cell and macrophage recruitment in mice (Pisanti et al., 2017a)
- Modulation of IL-10 and IL-12 in macrophages via CB2 (Pisanti et al., 2017a)
- CBD reduces intestinal permeability, and increases T regulatory cells (Becker et al., 2019)
- CBD reduces intestinal hypermotility (Abalo et al., 2012)

Metabolic Disease

200mg CBD / day did not have any effect on markers of inflammation, blood lipids, or blood glucose after 13 weeks in 62 type 2 diabetes patients compared to placebo. However, CBD significantly decreased resistin (-898 pg/ml) and increased glucose-dependent insulinotropic peptide (21.9 pg/ml) compared to placebo. This may hint at a greater clinical effect with higher doses (Jadoon et al., 2016).

200, 400 and 800mg CBD / day taken for 8 weeks did not improve liver triglycerides in 25 patients with fatty liver compared to placebo (clinical trials/NCT01284634).

Suggested Mechanism(s) of Action

- CBD 5mg/kg significantly reduced the incidence of diabetes (30% Vs 86%) in diabetic mice. Peritoneal macrophages taken from CBD treated mice expressed significantly reduced TNF-α and increased IL-10 (Weiss et al., 2006).
- CBD at 3mg/kg for 4 weeks reduced hepatic triglycerides in obese mice, which may be due to increased AMPK activity in human HH-L5 hepatocytes (Silvestri et al., 2015).
- In Zuzker diabetic rats, 10 mg/kg CBD reduced hyperinsulinemia (Wheal et al., 2017). CBD is a negative allosteric modifier of CB1, and shows similar effects as CB1 antagonist Rimonabant to reduce pancreatic insulin secretion (Bermudez-Silva et al., 2016).

Substance Abuse

24 smokers receiving inhaled doses of 400 μg CBD per application reduced cigarette consumption by up to 40% after 1 week compared to placebo (Morgan et al., 2013).

A repeated measures study found that smoking high CBD : THC cannabis was associated with lower dependence scores compared to high THC : CBD cannabis in 94 regular smokers (Solowij et al., 2018).

Suggested Mechanism(s) of Action

- CBD reduces Anandamide re-uptake, and increases CB1 activation (Ligresti, De Petrocellis and Marzo, 2016).
- CBD activates 5HT1A to regulate serotonin signalling, which may reduce reward seeking (Ligresti, De Petrocellis and Marzo, 2016).

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Chapter 4: Pharmacology

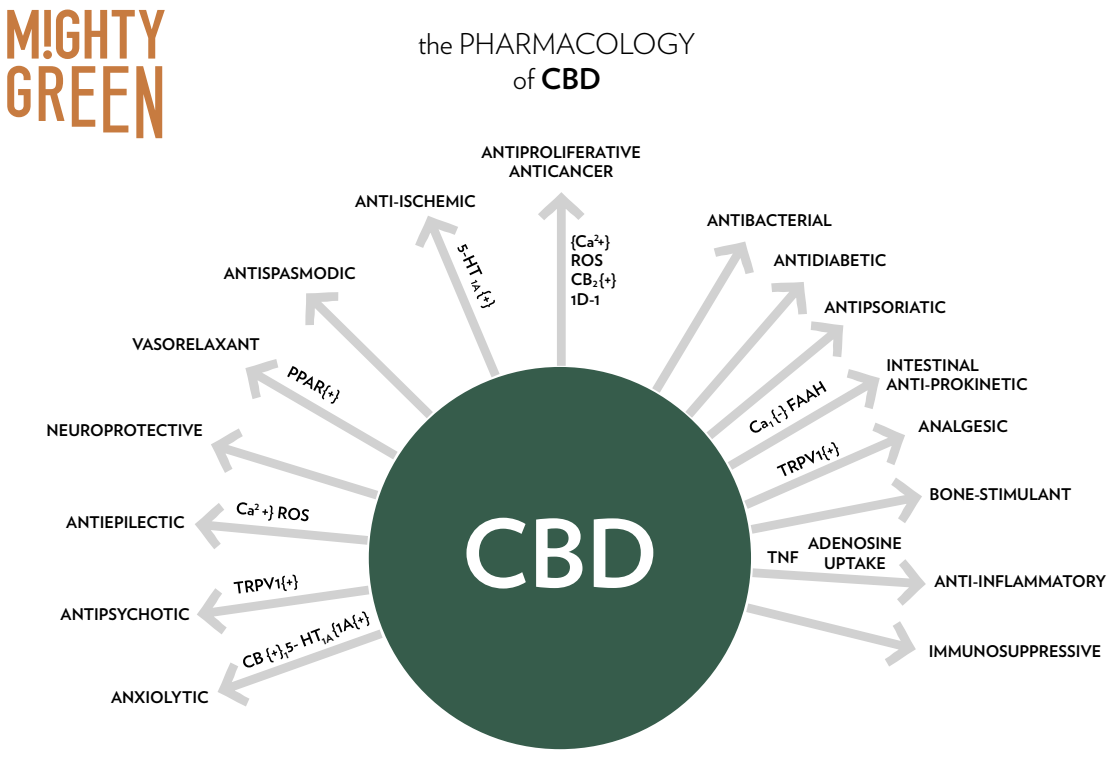
Anecdotally, CBD has been heard to help different people with different ailments. Research with CBD is still very much based in the basic sciences, using animal studies as a means to discover the mechanisms at work behind its seeming ubiquity within the body.

CBD is a cannabinoid, a class of compounds which share similar biological activity to the endogenous lipid signalling molecules inherent within the human body, known as Endocannabinoids.

Endocannabinoids act as messengers far and wide throughout the human body, both within and outside of their specific cannabinoid receptors.

CBD is an analogous compound to the endocannabinoids Anandamide and 2-Arachidonoylglycerol, and can therefore perform similar signalling functions across myriad communication networks.

CBD is a promiscuous compound, and interacts with numerous different receptors, having a diverse impact on human physiology.



Cannabinoid Receptors

These are receptors which specifically recognise the cannabinoids found within Cannabis Sativa L.

Cannabinoid receptor 1 (CB1)

CB1 was the first cannabinoid receptor to be discovered, and is one of the most prominent cannabinoid receptors found in the human body.

CB1 is abundantly expressed throughout the brain, nervous system, and within several organ systems. Minor expression of CB1 can be found within the immune system.

Functions of CB1 include:

Mood
Memory
Appetite
Sleep
Metabolism
Pain
Digestion
Thermoregulation

Unlike other cannabinoids and endocannabinoids, CBD has weak affinity for CB1 and does not activate it.

CBD was found to negatively modulate the response to CB1 agonists THC and 2-AG in mice and humans. Both negative allosteric modification, as well as a weak antagonism of CB1 (Morales, Hurst and Reggio, 2017) may account for some of the effects of CBD, such as the reduction of anxiety produced from a THC high (Englund et al., 2013).

In cases of obesity and diabetes where endocannabinoids are overabundant, CBD may help to negatively modulate over activation of CB1. However, this has yet to be clarified.

Cannabinoid receptor 2 (CB2)

CB2 is most abundant within the immune system, and its expression is modest within organ systems. CBD does not activate CB2 receptors, but has properties as a weak antagonist and negative allosteric modulation (Morales, Hurst and Reggio, 2017).

CB2 principally regulates pain and inflammation, and it's possible CBD exerts some immunomodulatory effects via this receptor, although there are multiple other targets.

G Protein-Coupled Receptors (GPR)

After the primary cannabinoid receptors CB1 and CB2, research has established the existence of cannabinoid like receptors called GPR's.

GPR55

GPR55 is found mainly in the brain, particularly the cerebellum. It's also found on both bone forming and bone degrading cells, suggesting it plays a role in bone architecture.

It also occurs in metabolic tissues, such as the hypothalamus, gastrointestinal tract, pancreas, liver, white adipose tissue, and skeletal muscle (Bazwinsky-Wutschke, Zipprich and Dehghani, 2019). GPR55 may play a role in energy metabolism, and affect food intake and body composition.

GPR55 has been associated with conditions such as cancer, metabolic syndrome, pain, vascular complications, motor functions and bone physiology (Morales and Patricia H Reggio, 2017).

When activated, GRP55 may have pro-cancerous effects. It has also been found at higher levels than usual in cases of colorectal cancer (Ramer, Schwarz and Hinz, 2019).

CBD has shown activity as an antagonist of this receptor, meaning it inhibits its activity (Morales, Hurst and Reggio, 2017).

In line with this, CBD has shown to inhibit the initiation of colon cancer via blocking GRP55 (Ramer, Schwarz and Hinz, 2019).

GPR18

GPR18 is found mainly within the lymphatic system, and in the lungs, brain, spleen and reproductive tissues (Morales and Patricia H Reggio, 2017), (Guerrero-Alba et al., 2018).

This receptors activity is suggested to be involved in the promotion of cancer, metabolic conditions, intraocular pressure (Morales and Patricia H Reggio, 2017), immune activity, inflammation and pain (Guerrero-Alba et al., 2018).

CBD is an antagonist at GPR18 (Morales, Hurst and Reggio, 2017), which may account for its role in inhibiting cancer progression, pain and inflammation (Pellati et al., 2018).

Transient Receptor Potential Channels (TRP)

Transient receptor potential channels regulate the flow of ions, such as calcium into cells. This is controlled by a family of specific receptors called TRP's.

The flow of ions into cells influences body functions like temperature, pressure and PH regulation, smell, taste, vision and pain perception.

TRPV

TRPV is a specific sub type of TRP known as a vallinoid receptor. Vanilloids are specific compounds that are recognised by this receptor, and as the name suggests, can be found in vanilla and also chillies.

TRPV expression has been characterised on neurones throughout the brain, immune cells and

blood vessels (Tsuji and Aono, 2012).

There are 4 types of TRPV. TRPV1 specifically regulates body temperature, the perception of pain, blood pressure, inflammation and psychotic state.

CBD has been shown to activate TRPV1 and increase calcium concentration into cells. CBD is also an agonist at TRPV2 and TRPV3 receptors (Morales, Hurst and Reggio, 2017).

CBD reduced psychosis and pain in animal models, which could in part be because of the activation of TRPV1 (Ruggiero et al., 2017). Activation of TRPV2 and 3 may play an additional role in reducing pain.

This mechanism may partly account for the reduction seen in these studies with CBD.

TRPA1

This receptor can often be found with TRPV1 on sensory neurones and can be activated by pungent compounds called isothiocyanates. These compounds are specific to plants such as mustard, garlic and onion.

TRPA1 is involved in the perception of inflammatory and chronic pain, and its activity may play a role in the several diseases.

CBD has been found to act as an agonist at this receptor (Morales, Hurst and Reggio, 2017), which again may account for its ability to reduce pain.

Peroxisome proliferator-activated receptors (PPAR's)

PPARγ

Peroxisome proliferator-activated receptor gamma is a variety of nuclear receptor that acts as a transcription factor to regulate gene expression.

PPARγ is found mainly within the liver, fat tissue, colon, kidney and macrophages (immune cells). It is found within most other tissues but to a lesser extent.

PPARγ is involved in fatty acid storage and glucose metabolism, in addition to inflammation and blood pressure (vasodilator).

It plays a role in several diseases including obesity, diabetes, CVD and cancer (O'Sullivan, 2016).

Activating PPARγ generally reduces (neuro)inflammation, blood sugar, cholesterol, blood pressure and blood brain barrier permeability (O'Sullivan, 2016).

CBD is an agonist of PPARγ (Morales, Hurst and Reggio, 2017), and has shown to reduce inflammation, cancer progression and blood pressure in animal models (O'Sullivan, 2016). Clinical research has yet to clarify this in humans.

Serotonin (5-HT) Receptors

Hydroxytryptamine (serotonin) receptors are a family of G-coupled protein receptors which are involved in the regulation of diverse physiological processes.

They are found far and wide within the central and peripheral nervous system, blood vessels, gastrointestinal tract and smooth muscle.

Serotonin receptors regulate numerous biological processes including appetite, mood, memory, learning, anxiety, sexual behaviour, addiction, blood pressure, sleep, thermoregulation and more.

Serotonin is a neurotransmitter that confers messages via these receptors to turn up or down the above biological processes.

5-HT1a

5-HT1a is one of over 14 subtypes of serotonin receptor. CBD has a particular attraction to 5-HT1a, as an agonist of this receptor (Morales, Hurst and Reggio, 2017).

The activation of 5-HT1a may account for the anti-anxiety, anti-emetic and mood enhancing effects seen with CBD (Soares and Campos, 2017). CBD-A also activates 5-HT1a but with a stronger binding affinity (Bolognini et al., 2013), which may prove additionally useful for managing anxiety and emesis.

GABA Receptors

GABA is the main inhibitory neurotransmitter in the central nervous system. Its corresponding receptor(s) are responsible for mediating neuronal signalling, acting as a chemical braking system.

GABAa is one specific receptor subtype which recognises GABA, and other select ligands. Its expression is predominantly centric to the brain and central nervous system, and to a lesser extent on endocrine tissues and immune cells.

GABA plays a role in:

6. Cognition
7. Anxiety
8. Sedation
9. Respiratory rate
10. Convulsion
11. Sleep

Similar to the classic GABAergic drugs, CBD is a positive allosteric modulator of GABAa receptors (Morales, Hurst and Reggio, 2017). In this way, CBD alters the GABAa receptor which increases its binding affinity for the GABA neurotransmitter. In effect, CBD amplifies the naturally calming, sedating effects of GABA (Bakas et al., 2017).

This may also account for the anti-anxiety effects of CBD, whilst also facilitating sleep.

Glycine Receptors (GlyRs)

GlyRs also play a large role in inhibitory neurotransmission, predominantly in the spinal cord and in the brain stem. They provide similar functions to the GABAa receptor.

GlyRs are thought to be involved in the perception of neuropathic and inflammatory pain. CBD is a positive allosteric modulator of α1 and α3 subunits of GlyRs (Morales, Hurst and Reggio, 2017), and may potentiate the inhibitory signal of GlyR agonists, such as glycine.

In this way, the modulation of GlyRs by CBD may offer enhanced resolution of pain (Xiong et al., 2012).

Opioid Receptors

These are a group of inhibitory G-protein coupled receptors, which are widely expressed throughout the brain, nervous and digestive systems.

CBD interacts with two specific subtypes of opioid receptor, as a positive allosteric modulator of both mu (μ) and delta (δ) opioid receptors (Morales, Hurst and Reggio, 2017).

Delta receptors play a role in pain perception, addiction, mood and convulsion. Mu receptors affect changes in intestinal motility, euphoria, pain perception, respiration and addiction.

It is via these receptors that CBD may play a role in analgesia and in addiction (Wiese and Wilson-Poe, 2018), (Hurd et al., 2015), (Viudez-Martínez et al., 2018) by reducing the rewarding properties of drugs and cravings.

Adenosine Receptors

These are a family of G-protein coupled receptors, with several subtypes. A1 and A2 receptors are expressed within the brain and regulate the release of excitatory neurotransmitters dopamine and glutamate. Both also regulate myocardial oxygen consumption and blood flow. A2 are specifically on in immune cells, which plays a broader anti-inflammatory role throughout the body.

Antagonism of A1 and A2 receptors by caffeine produces stimulant effects, and agonists of these receptors elicit reduced heart rate, vasodilation, and reduction of excitatory neurotransmission (Chen, Eltzschig and Fredholm, 2013).

Whilst CBD is only an A1 agonist (Morales, Hurst and Reggio, 2017), it also inhibits the re-uptake of Adenosine in the brain allowing it to have an indirect effect on additional adenosine receptors (Ibeas Bih et al., 2015).

This mechanism may partly contribute to anti-anxiety, anti-inflammatory and cardioprotective effects of CBD (Durst et al., 2007).

Anandamide Availability

CBD has the ability to indirectly modulate the endocannabinoid system, via influencing levels of the CB1 and CB2 receptor agonist, Anandamide (Leweke et al., 2012).

In order to act on nuclear receptors (like PPAR) inside a cell, Anandamide has to be chaperoned by a fatty acid binding protein (FABP). However, once inside the cell, Anandamide is broken down by its respective enzyme Fatty Acid Amide Hydroxylase (FAAH).

CBD increases levels of extracellular anandamide, as it competes for the same FABP. Additionally, CBD increases levels of intracellular anandamide by inhibiting FAAH (Deutsch, 2016).

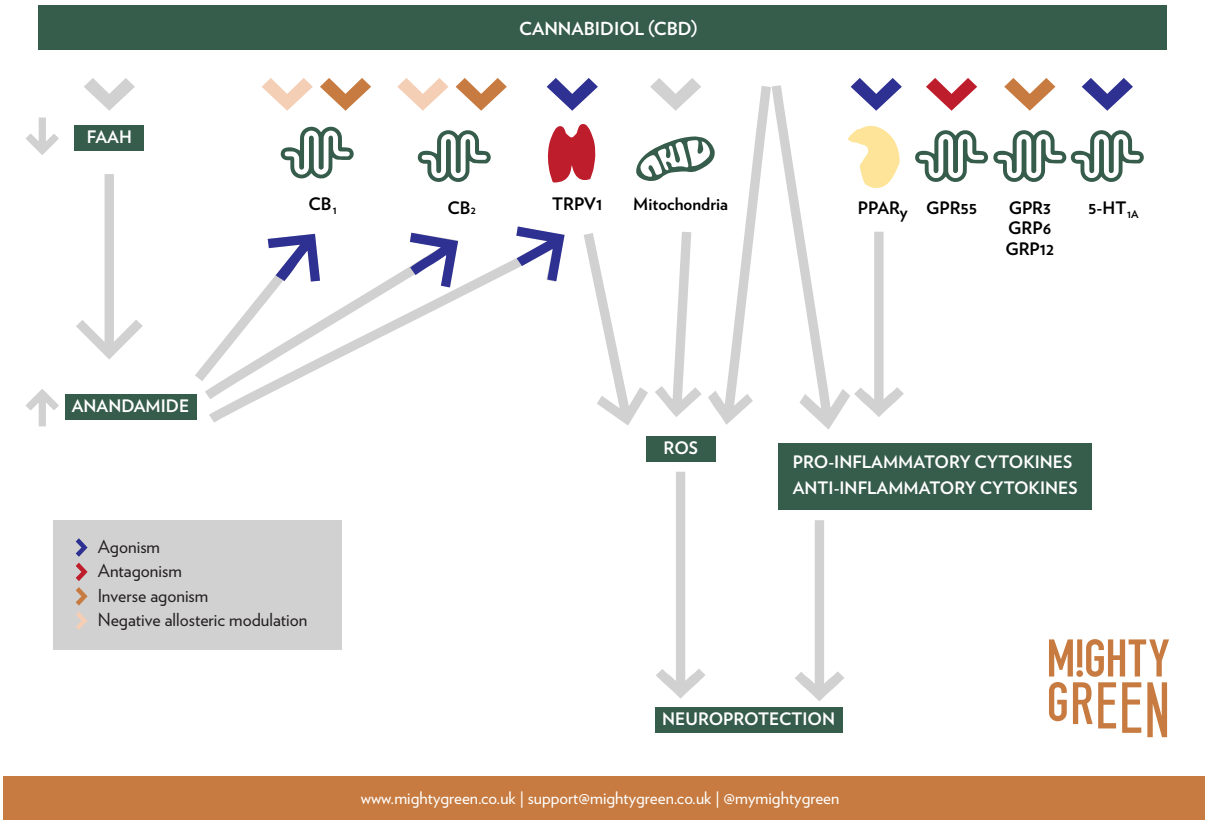
Anandamide plays a diverse role in human physiology, and increasing its availability enhances endocannabinoid tone in a way that may be ubiquitously beneficial, such as in neuropsychiatric, cardiovascular, autonomic, metabolic, and inflammatory states (Leweke et al., 2012), (Scharf, 2017).

Anti-Inflammatory

Cycloxegenase-2 and 5-lipoxygenase are enzymes which produce pro-inflammatory messengers called prostaglandins and leukotrienes. CBD exerts its anti-inflammatory actions by blocking these enzymes (Costa et al., 2004), (Burstein, 2015).

CBD also reduces the expression of other pro-inflammatory messengers TNF-α, IL-6, IFN-β, IL-1β and NF-kB, and increases the expression of anti-inflammatory cytokines such as IL-4 and IL-10 (Pisanti et al., 2017), (Peres et al., 2018).

CBD exerts these immuno-modulatory effects via multiple receptors expressed on immune cells and may prove clinically useful for a host of inflammatory conditions.



Antioxidant

CBD has displayed potent antioxidant properties (Hacke et al., 2019), and donates electrons to neutralise various species of free radical. CBD has been shown to reduce parameters of oxidative stress (Nagarkatti et al., 2009), (Rajesh et al., 2010). It also up-regulates the production of the antioxidant enzyme superoxide dismutase (Peres et al., 2018).

CBD may prove useful in conditions associated with oxidative stress, such as in diabetic complications and hypertension (Booz, 2011).

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Chapter 5: CBD & The Law

As a healthcare professional, it's important that you know what you're giving to your clients is safe, effective and in the case of cannabis related products, legal.

The CBD market in the UK is an emerging and rapidly growing one, with very little regulation currently in place.

The rate of CBD use has doubled in the UK from 2017-2018, from 125,000 to 250,000 users, with an estimated adoption rate of new users of 1K new users per month. Market research commissioned by the CMC estimates that by 2025, the UK CBD market is estimated to be worth £1 billion.

That's a lot of new consumers, and you bet there's a lot of businesses jumping at the opportunity to meet those demands for a piece of the pie. However, due to the novelty of CBD and cannabis-based products, there's a fairly loose regulatory environment surrounding quality control in the UK market.

This article will cover the current legislation and guidelines around CBD in the UK, and how quality control can be assured in the current regulatory environment.

How Is CBD legal?

It's a tricky one for a lot of folks to wrap their head around though, since CBD is derived from cannabis plants.

However, there are several different types of cannabis plant, which are classified based on the variation of their chemical constituents.

The most renown constituent of cannabis plants is the psychoactive compound called THC. In the UK, THC is a controlled substance under the Misuse of Drugs Act 1971 because it is the compound in cannabis that gets user 'high'.

Unlike THC, CBD is non-psychoactive and does not get users high.

Whilst cannabis also contains CBD, its typically off limits because of the co-occurring THC which is illegal. Fortunately, there is a particular type of cannabis plant which naturally produces very low levels of THC. This variety is commonly known as Hemp, which contains < 0.2% THC.

This is the limit set by the Misuse of Drugs (Fees) Regulations 2010 because it is not a sufficient concentration of THC to induce psychoactive effects. THC exceeding these limits may lead to addictive and psychotic behaviours in some people when consumed, hence why it has been outlawed.

In the UK, CBD is legal so long as it has been obtained from the 'Hemp' variety of cannabis, which by nature complies with restrictions applied to THC.

'Marijuana' is another non-botanical classification for another variety of cannabis, which by nature produces THC in quantities that authorities deem as illegal (> 0.2% THC). Marijuana can produce THC in amounts up to 30%, which is more than enough to produce a psychoactive effect in its users.

CBD Classification

Another reason CBD can be sold legally in the UK is because of the way it is classified and presented to consumers.

CBD as a Food Supplement

CBD can be sold legally so long as its classified as a food supplement, which poses restrictions as to what claims can be made about what it does.

According to the FSA, no health claims relating to Hemp or CBD are permitted under Regulation (EC) No 1924/2006.

"A 'health claim' means any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

A health claim may refer to a reduction in disease risk, or how a food or its ingredient(s) support function(s) within the body.

Most CBD in the UK is sold in wellness and health food outlets and websites, without any claims as to how it interacts with aspects of human health.

That also goes for medical claims, too. According to the FSA, it is not permitted to make a medical claim about food. Since CBD is classified as a food supplement, this also prevents any medical claims being made around its use.

"Medicinal claims are those which attribute to food the property of preventing, treating or curing a human disease"

Claims such as 'lowers anxiety' or 'anti-inflammatory' or 'treats seizures' cannot be made.

It is important that we don't make health claims about CBD to our clients.

Changes to CBD Classification: Novel Foods

This year the EU has moved to revise its stance on CBD containing products in an attempt to bring greater scrutiny to the market. The FSA stated that it strives to "clarify how to achieve compliance in the marketplace in a proportionate manner".

Instead of food supplements, CBD containing foods and supplements may be considered as 'Novel foods'.

The definition of a novel food:

"Foods or food ingredients which do not have a history of consumption prior to May 1997 in the EU"

Since many CBD products use supercritical Co2 extraction, it is hard to argue that CBD would have been consumed in this form before such technology existed. Much of the accounts of Hemps use in traditional medicine refers to extraction using food-based fats and ethanol preparations (Russo, 2005, 2007).

If CBD is to be classified as a novel food, products would have to undergo a lengthy and potentially costly process of scientific risk assessment by the European Food Safety Authority to determine:

1. Any risk to public health
2. The product is not nutritionally disadvantageous when replacing a similar food
3. It is not misleading to the consumer

One application by Cannabis Pharma has been submitted for a CBD food supplement for adults, with a daily recommendation of 130mg. If successful, CBD will be permitted on the novel foods list which may help clarify conditions of use, maximum intakes and labelling requirements.

CBD as a Medicine

Under special circumstances, CBD can also be classified as a medicine. Under this classification, medical claims may be permitted. However, it is highly unlikely any organisations other than those in the pharmaceutical domain will achieve this.

According to the Medical Products and Healthcare Agency (MHRA):

"We have come to the opinion that products containing cannabidiol (CBD) used for medical purposes are a medicine. Medicinal products must have a product licence (marketing authorisation) before they can be legally sold, supplied or advertised in the UK, unless exempt. Licensed medicinal products have to meet safety, quality and efficacy standards to protect public health".

An example of this kind of product is Epidiolex, a highly purified plant derived cannabinoid medicine produced by GW Pharmaceuticals in the UK.

Epidiolex is a prescription form of cannabidiol (CBD), which according to the Guardian has been authorised by the European Medicines Agency (EMA) and the European commission for Lennox-Gastaut syndrome (LGS) and Dravet syndrome - two rare forms of epilepsy.

Quality Control Standards

In the current UK market, a lot of CBD products sold as food supplements may fall short of general, but not official standards expected by consumers.

Trading Standards is the authority that will likely oversee the CBD retail market in the future. A regulatory framework has yet to be established by Trading Standards, until guidance from the MHRA and other authorities has become clearer.

This basically means that consumers have no legal quality guarantees. Due to this lack of regulation around quality control, some brands may make false claims as to the CBD content of their products, and use language on their labels that is misleading.

For example, providing lab reports to clarify the dosage of CBD stated on labels is not yet compulsory, or even industry standard. Therefore, consumers may receive much less CBD than promised.

Each batch of Mighty Green's products are laboratory tested and available to view on our website.

A study of 14 commercially available CBD oils sold in Europe revealed that at least 9 of them contained levels of CBD that differed significantly from the declared amount (Pavlovic et al., 2018). Three of those oils had CBD concentrations that varied by up to 35% from the amount promised.

The same study also found that certain products contained lipid peroxidation products. These are fats that have been damaged by light, air or heat and may reduce the therapeutic efficacy of the product.

Cannabinoid testing is also important for assessing the levels of THC contained in the products. It is not uncommon to find products that exceed the legal limits of THC. This may put consumers at risk from experiencing the psychoactive effects of THC, which for some may be unpleasant.

Some opportunists have also taken advantage of the confusion consumers face when trying to understand tricky nomenclature around Hemp.

Hemp seed oil is often sold under the guise of 'Hemp oil'. Since new users associate CBD with Hemp, they are often misled into thinking they are actually buying CBD oil. Unlike CBD oil which is extracted from the CBD containing parts of Hemp (stalks, stems, leaves and flowers); Hemp seed oil contains no CBD whatsoever, and only comes from the seeds.

Legality of Other Cannabinoids

Most CBD is extracted from Hemp by supercritical Co2 extraction, which yields what is known as a full or broad-spectrum extract. Besides just containing CBD, this extract contains other cannabinoids such as CBG, CBC, and other beneficial compounds such as terpenes - the full spectrum.

Much like THC, other cannabinoids can also fall under controlled status, either because they are also psychoactive, or for reasons that haven't yet been made clear.

CBN is another cannabinoid, which was found by the Advisory Council on the Misuse of Drugs to be psychoactive and therefore illegal:

"Cannabinol and 'Cannabinol derivatives' are controlled by the Misuse of Drugs Act 1971 as Class B drugs"

THCV is another cannabinoid which is controlled, because it is a derivative of CBN. According to the home office:

"THCV or 'tetrahydrocannabivarin' is a cannabinol derivative which is listed as a Class B drug under the Misuse of Drugs Act 1971"

Before choosing an oil for your clients, always refer to the lab tests for clarity as to what is safe and legal.

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Chapter 6: CBD Dosing Guidelines

The activity of your endocannabinoid system is a reflection of the highly variable biochemical uniqueness that exists between you, me and the next person. That's why a one size fits all approach to using CBD will produce different results for everyone.

Research is useful, but not as relevant as we'd like.
Scientific research typically applies standardised doses to people grouped by medical condition. This is problematic because no one experiences a shared condition in the same way as someone else does.
For example, there's no specific dose for managing specific symptoms, like pain or anxiety, because they are highly subjective experiences.

Having said that, the studies that do currently exist are a good rule of thumb to gauge the ballpark figures for:

- A minimum therapeutic effect
- Establishing tolerable upper limits (safe doses)

CBD hasn't yet been allocated an official recommended daily allowance, mainly because it's a phytochemical, not a vitamin or mineral.

Now we can estimate the smallest amount needed to produce an effect. This forms the initial guidelines by which you can explore your therapeutic window.

You can use yourself as a guinea pig here, start low and work your way up. **A standard dose could be ~ 25 mg, but you may choose to start at 5 mg and work your way up.**

As practitioners, we would not recommend more than 200mg daily. (Otherwise we are moving into pharmaceutical levels).

CBD doses of up to 300 mg daily for up to 6 months have been safe (Cunha et al., 1980), and higher doses of 1200-1500 mg have been used for up to 4 weeks (Zuardi et al., 2010).

These are high doses that we would not recommend, but give us confidence in the tolerable upper limit.

Body Weight As A Rule of Thumb

This method is much like using BMI to assess body composition – it is useful, but far from perfect. Just like BMI, going by weight alone fails to account for genetic differences in your ECS and metabolism that influences the effects CBD may have.

Even if you share the same body weight as someone, you could have a totally different effect from CBD.

Your response will vary based on your unique body composition and:

- **Endocannabinoid tone** (synthesis, degradation and signalling of EC's)
- **Metabolic activity of liver enzymes** (CYP) which metabolise cannabinoids
- **Nutritional Status** (omega 3:6 consumption notably)
- **Stress** (impacts EC tone)
- **Sleep** (also impacts EC tone)

To find your optimal dose, you need to find the window between the smallest dose which produces a meaningful effect, and the point where your response starts to plateau as the dose increases. This you could call the upper limit of the therapeutic window.

Finding your window helps avoid wasting your precious CBD and prevents overshooting a therapeutic sweet spot.

CBD has no official Tolerable Upper Limit (maximum safe dose), but is generally well tolerated. That's why it is a good idea to have some idea from the literature just to be safe.

How To Take CBD

One of the most popular ways to ingest CBD is by using an oil. These come with a glass pipette which administers CBD with a carrier oil in small droplets. Place drops under the tongue.

Alternatively, you can get capsules which are already pre-dosed so taking fixed doses consistently is easier. Capsules tend to come in ranges from 10-50mg, so experimenting with doses is slightly less flexible.

It might be easier to use oils and tinctures at first as you can increase and decrease the dose with more precision.

You may have noticed that CBD can be referred to as a percentage as well as in milligrams (mg). Confusing, right?

Whilst knowing the percentage is handy to assess the general potency you are getting, measuring doses in mg is more practical. This way you can also go by doses used in research as well, as CBD is mostly referred to in mg.

To most accurately dose CBD, **knowing how much CBD in mg/drop** can help you find your sweet spot with plenty of room for exploration. This is why we always state mg/drop on our products.

Tracking Your Way To Success

Once you have established mg/drop, you can start to track how you respond to different doses, and establish whether it is best to:

- Dose in response to symptoms
- Dose periodically throughout the day
- Dose with food
- Dose Morning or Night

There's no one right way to use CBD as it works very subjectively. After a little experimentation, you can find how much, when and with what CBD works best for you.
Use a tracking diary or sheet to remember what doses you have used; at what time and the experience you notice for that particular dose – for example, pain relief 6/10.

You may also like to document a little bit about what is going on in your day to see how that affects how you respond to your CBD dose – for example, you had a particularly stressful day, which made it harder for your pain to subside. You may find you need a slightly higher dose on more stressful days.

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The end of part 1....

Thank you for reading. We would love to hear your feedback and if there are any specific areas you would like covered in Part 2.

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In the meantime, look out for our newsletters!