GROW
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Medical cannabis and chronic pain

An introductory overview for healthcare professionals

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Introduction to Grow Pharma

Grow Pharma (www.growgroupplc.com) is the largest and fastest growing provider of cannabis-based medicinal products (CBMPs) in the UK. Grow Pharma offers training, support, and education on CBMPs, and can also assist with the regulatory guidance associated with the prescribing of these unlicensed medicines.

For those interested in this rapidly growing field, there are several ways to become involved:

- Join one of the medical cannabis clinics that Grow partners with
- Add medical cannabis to the armamentarium of medicines prescribed in an existing private practice
- Set-up a new medical cannabis clinic
- Refer appropriate patients to one of the specialist medical cannabis clinics

Grow Pharma can support healthcare professionals in pursuing any of the above options.

For further information and support, please contact one of the team members below

Pierre van Weperen – CEO Grow Pharma
pierre.vanweperen@growbiotech.com

Anup Shah – Business Development Manager
anup.shah@growbiotech.com

Luca Marelli – Medical Science Liaison
luca.marelli@growbiotech.com

Alex Fraser – Patient Access Lead
alex.fraser@growbiotech.com

Introduction to medical cannabis in the UK

On the 1st November 2018, CBMPs were rescheduled under the Misuse of Drugs Regulations 2001 from Schedule 1 to Schedule 2, specifically for when made to pharmaceutical standards.[1]

CBMPs can now therefore be prescribed by a consultant, when appropriate, within their specialty area when there is an unmet clinical need. This can be through a private or NHS clinic but must be on a private (FP10PCD in England) prescription.

There are three licensed cannabis medicines in the UK:

- Sativex (nabiximols) – an oromucosal spray for multiple sclerosis (MS)
- Epidiolex (cannabidiol) – used to treat rare forms of epilepsy
- Nabilone – for severe nausea and vomiting associated with chemotherapy

There are currently no licensed cannabis medicines indicated for the management of chronic pain. However, despite this, chronic pain is the most common reason for patients taking cannabis for medical purposes.[2,3]

Variable	All (N=1,145)
Primary illness or medical condition you currently treat with medical cannabis	n (%)
Unknown	1
Anxiety disorder	109 (9.5)
Arthritis	81 (7.1)
Brain injury	3 (0.3)
Cancer or leukemia	17 (1.5)
Chronic pain	787 (68.8)
Crohn's disease	6 (0.5)
Diabetes	2 (0.2)
Eating disorder	2 (0.2)
Epilepsy	5 (0.4)
Gastrointestinal disorder	6 (0.5)
Headache	25 (2.2)
Insomnia	57 (5.0)
Movement disorder	9 (0.8)
Osteoporosis	1 (0.1)
Psychiatric or mental health disorder	4 (0.3)
PTSD	8 (0.7)
Seizures	1 (0.1)
Other	21 (1.8)

Figure 1 - Medical cannabis patterns of use[2]

To aid access to these medicines, clinics have been set-up specifically for treating conditions which may benefit from CBMPs, including chronic pain. Patients can self-refer to these specialist clinics or can be referred by their doctor.

The Endocannabinoid System (ECS)

The ECS was discovered in the 1990s[4,5] and consists of cannabinoid receptors, endocannabinoids, and their metabolic enzymes.[6]

Cannabinoids are produced endogenously by all vertebrates, with Anandamide (AEA) and 2-Arachidonoylglycerol (2-AG) being the most well-known.[7] There are two main cannabinoid receptors, CB1 and CB2. CB1 receptors are found mainly in the central nervous system (CNS), whereas CB2 receptors are predominantly expressed in the peripheral nervous system (PNS) and other tissues in the body, as well as immune system cells.[8]

The ECS regulates many physiological processes including inflammation and pain perception, immunity, neuropathy and metabolism.[6]

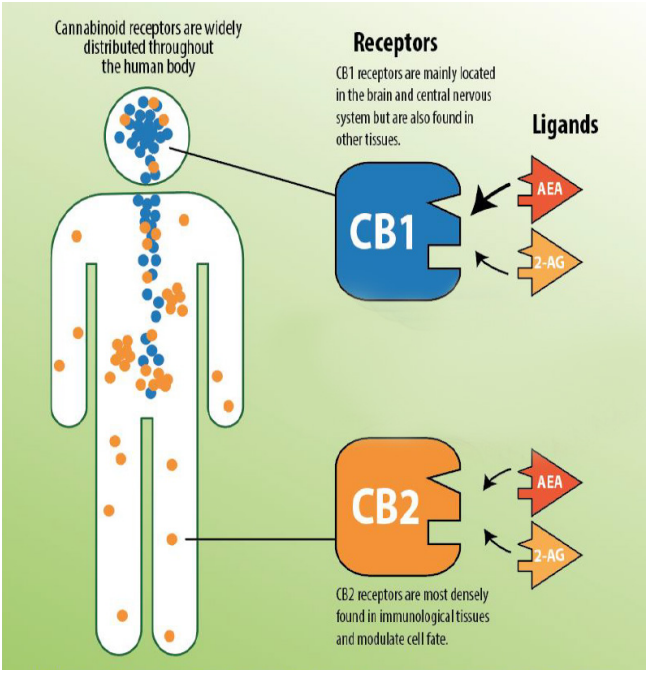

Figure 2 – The Endocannabinoid System (ECS)[6]

Phytocannabinoids – THC and CBD

Cannabinoid compounds present within the cannabis plant are known as phytocannabinoids. There are around 120 different phytocannabinoids in the cannabis plant.[9] Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant, most studied and believed to be the most important clinically.[10]

THC produces psychoactive and other physiological effects – such as on pain and appetite – through its partial agonism of CB1 and CB2 receptors.[11]

CBD is not psychoactive and does not bind directly to CB receptors.

Instead, it can produce antipsychotic, anxiolytic effects through negative allosteric modulation of CB1 receptors, as well as additional effects via interactions with other receptor systems, including TNFα and 5-HT_{1A}. [12,13,14]

Overall, the effects of CBD overlap with those of THC despite a distinct pharmacological profile.

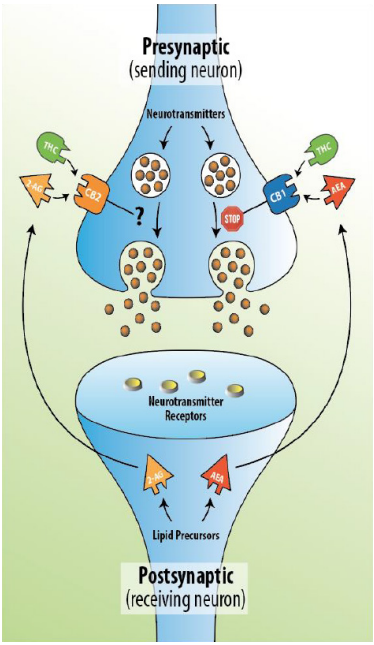

Figure 3 – Phytocannabinoid interactions at the synapse[6]

This is likely due to CBD acting on pathways that enhance the availability of cannabinoids at the synapse, such as inhibition of FAAH (an enzyme that breaks down AEA). [15]

The combination of THC and CBD is thought to have a synergistic effect in which other phytocannabinoids possibly participate. This synergism gave rise to the theory of the 'entourage effect', which emphasises the benefits of cannabis use over the use of isolated synthetic cannabinoids.[16]

Routes of administration

The most common methods of medical cannabis administration are the inhaled (via a vaporiser), oral and sublingual routes.[17] Smoking medical cannabis is illegal in the UK.

The oral route has the slowest onset of action (60–180mins) and the longest duration (6–8hrs), while inhalation is the most rapid (5–10mins) but has the shortest-lived (2–4hrs) effects;[18] the sublingual route falls in-between.

As a result, the oral and sublingual routes tend to be preferred for the daily management of chronic pain, while the inhaled method is more suitable as an additional as required (prn) option for managing break-through symptoms.[19]

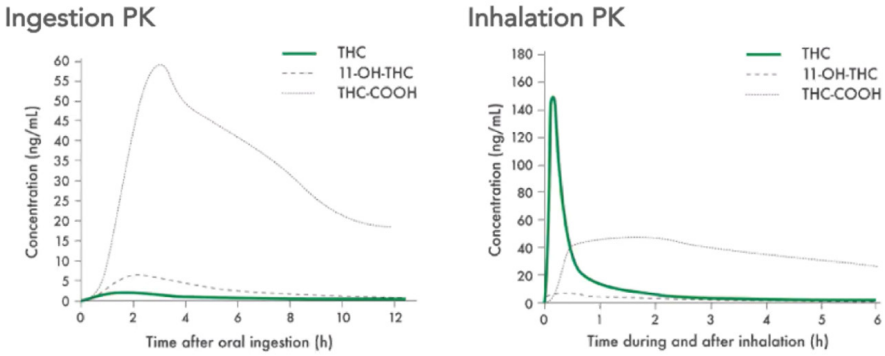

Figure 4 – The pharmacokinetics associated with different routes of administration[20]

The THC:CBD ratio

Response to cannabis is individualised so there is unlikely to be one THC:CBD ratio or dose that is suitable for all patients with a particular condition. This is due to the large number of compounds in cannabis, their wide-ranging effects on receptors and cells in different parts of the body, and the variable rate at which they are metabolised.[21] It is likely that an individual's own endogenous levels of endocannabinoids (and subsequent activity of the ECS) will impact their response to CBMPs.

A recent publication featuring a global panel of experts recommended that most patients with chronic pain should be started on a CBD-predominant product (10mg/day). If necessary, the CBD dosage and/or THC component (starting dose: 2.5mg/ day) can then be gradually increased until a balance between satisfactory symptom control and minimal adverse effects is reached.[19]

The same publication also advised that when initiating THC, clinicians may consider starting the first dose in the evening to limit potential issues with workplace functioning and driving, as well as potentially aiding sleep quality; a common issue among patients suffering from chronic pain.[19]

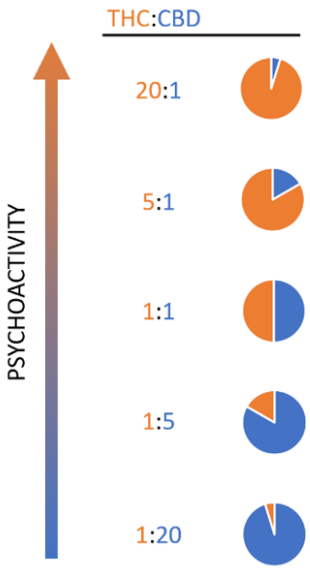

Figure 5 – Depiction of different THC:CBD ratios and their levels of psychoactivity

The ECS and chronic pain

The ECS has connections with both ascending and descending pain pathways, with CB1 and CB2 receptors present at all three levels of pain processing – in the periphery, spine and supraspinal sites.[22]

In the periphery, CB receptor activation suppresses allodynia and hyperalgesia related mechanisms. In the spine, the ECS is linked to windup and central sensitisation related mechanisms which are implicated in chronic pain. In the CNS, CB1 and CB2 receptors are especially active in pain-related brain areas, such as the periaqueductal grey matter, ventroposterolateral nucleus and the thalamus.[23,24]

In addition, non-CB receptors with which cannabinoids can interact such as TNFα, TRPV and 5-HT are also known to be implicated in pain signalling.[23]

Taken together, this provides the rationale for investigating cannabis as a potential option in the management of chronic pain.

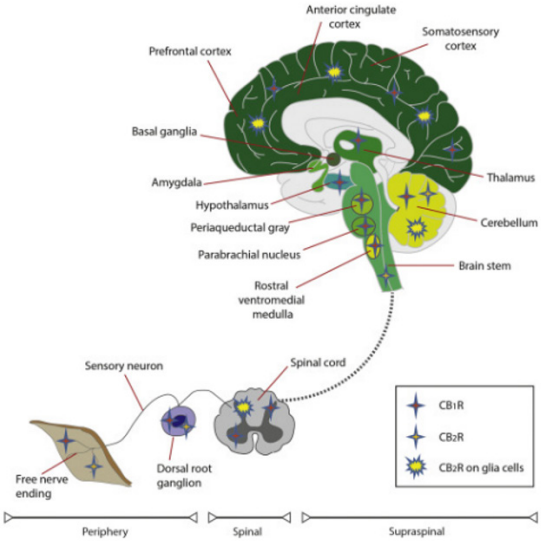

Figure 6 – Cannabinoid receptor distribution throughout the pain pathways[25]

Medical cannabis for the management of chronic pain

The antinociceptive actions of THC and CBD have been demonstrated in preclinical models of both inflammatory and neuropathic pain.[24] There have been a number of clinical studies investigating the effects of cannabis – as well as its potential capacity to reduce concurrent opioid usage – in patients suffering from chronic pain. Three of these trials are briefly outlined below, accompanied by a more comprehensive list in the next section.

A 2019 randomised controlled trial (RCT) found that vapourised administration of 22:1 and 13:18 THC:CBD preparations – but not 1:18 – caused a significant increase in the pressure pain threshold compared to placebo in chronic pain patients with fibromyalgia.[26]

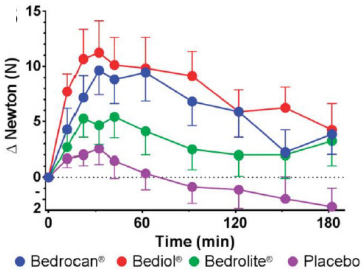

Figure 7 – The effects of cannabis (**purple** – placebo; **green** – 1:18; **red** – 13:18; **blue** – 22:1) on pressure pain threshold[26]

An observational study evaluating the impact of cannabis use in subjects suffering from chronic pain over a 6-month period found that relative to baseline, patients exhibited improvements in pain as well as sleep, mood, anxiety, and quality-of-life (QoL).[27]

A recent prospective study conducted in Canada reported statistically significant improvements with medical cannabis in all QoL domains over a 6-month period, alongside a 78% reduction in mean opioid dosage (MME) and an 84% reduction in the Defined Daily Dose (DDD) of non-opioid medications.[2]

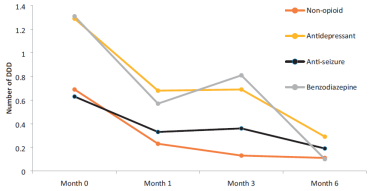

Figure 8 – Co-medication changes over 6 months[2]

The evidence gathered thus far has been evaluated in numerous systematic reviews and formed the basis for the recommendations outlined in several of the most recent international pain guidelines.

A 2015 systematic review published in JAMA commented that most trials are small and inconclusive showing numerical trends, often not reaching statistical significance, however when considered as a whole, they are suggestive of an effect. The report concludes that there is "moderate" quality evidence to support the use of CBMPs for the treatment of chronic pain.[28]

A 2017 NEJM publication discussing strategies for combating the opioid epidemic highlights that there is "strong" evidence for the efficacy of cannabinoids in treating pain.[29]

The National Academies of Science, Engineering and Medicine (NASEM) 2017 report[30] stated that there is "conclusive or substantial" evidence that cannabinoids are an effective treatment for chronic pain in adults. Other guidelines such as the European Pain Federation (EFIC) statement in 2018[31] and the Canadian Pain Society consensus statement in 2017[32] position cannabinoids as a 3rd line option for the treatment of chronic pain.

A 2021 BMJ guideline issued a "weak" recommendation stating that "people living with chronic pain should be offered a trial of non-inhaled medical cannabis if standard care is not sufficient".[33]

Chronic pain studies

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Safety considerations

Patients receiving CBMPs commonly experience transient adverse events (AEs), however the incidence of serious AEs is generally not significantly different compared with control individuals.[34] AE profiles from real-world studies broadly correlate with those of clinical trials and are generally dose-dependent, with dizziness, dry mouth and somnolence commonly reported.[35]

In terms of toxicity, the median lethal dose (LD50) versus standard daily human intake for THC is much higher than that for many other substances, including all opiates studied.[36]

In 2018, the Office for National Statistics reported that opiates were a factor (not necessarily attributable) in 2208 deaths in England and Wales, compared to 22 deaths with cannabis.[37] CB1 receptors are not expressed in the brainstem, which may explain the lack of cannabis-related fatalities due to respiratory depression.[38]

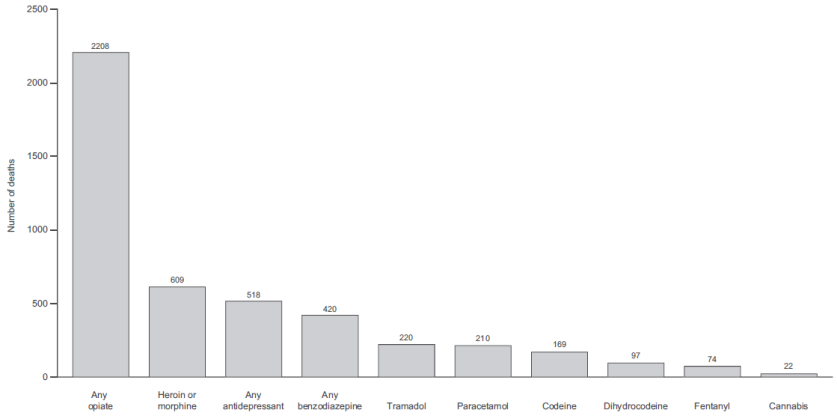

Figure 9 – Number of deaths related to selected drugs – where the drug was listed on the death certificate – in England and Wales in 2018[37]

Sativex contains both THC and CBD, so although it is licensed for MS, its summary of product characteristics (SmPC) serves as a useful reference.
Sativex Oromucosal Spray SmPC. Available at: https://www.medicines.org.uk/emc/product/602/smpc#gref (accessed 22 September 2021)

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