GROW
PHARMA

Medical cannabis and inflammatory bowel disease

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

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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 inflammatory bowel disease (IBD). 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]

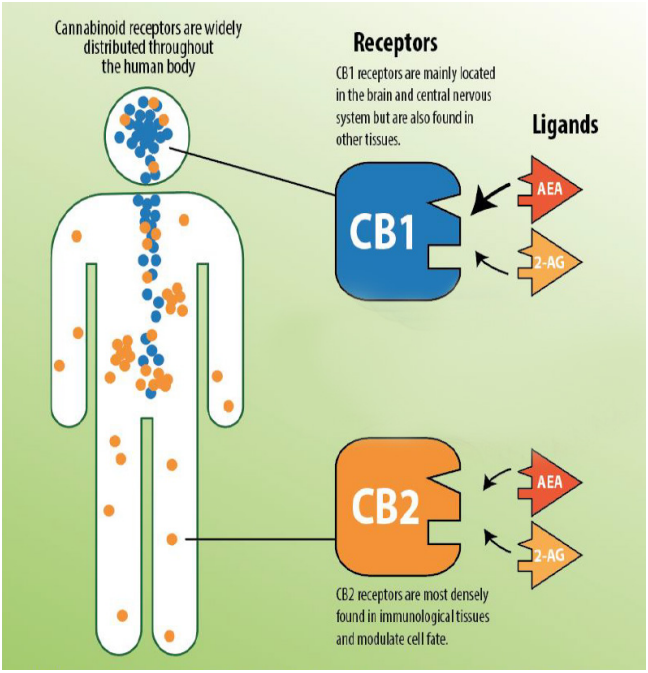


Figure 2 – The Endocannabinoid System (ECS)[6]

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]

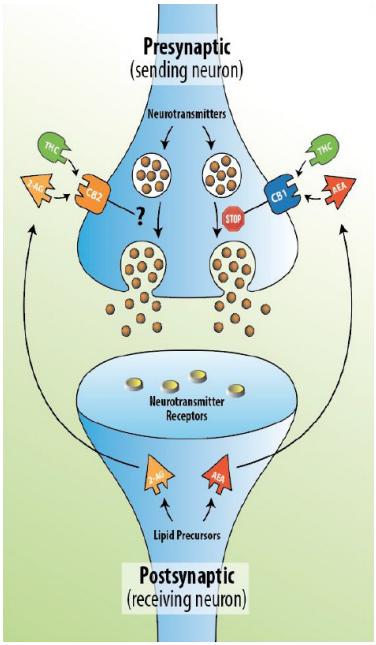


Figure 3 – Phytocannabinoid interactions at the synapse[6]

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.

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 conditions, while the inhaled method is more suitable as an additional as required (prn) option for managing breakthrough symptoms.[19]

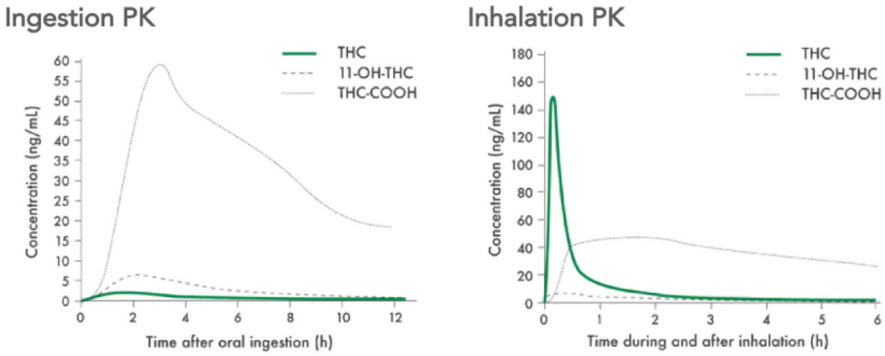


Figure 4 – The pharmacokinetics associated with different routes of administration[20]

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]

No standardised dosing regimen currently exists for managing IBD with CBMPs. However, guidance can be gleaned from recommendations for chronic pain. 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]

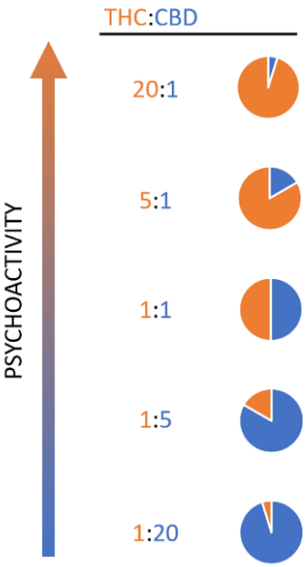


Figure 5 – Depiction of different THC:CBD ratios and their levels of psychoactivity

The same publication also advised that when initiating THC, there is the potential to prescribe a cannabis preparation containing a higher THC dose in the evening and a lower THC dose during the day to aid with occupational and carer responsibilities and driving.[19]

Chronic pain in patients with IBD

Symptoms dominate IBD disease activity indices, but the primary target for treatment is inflammation of the gut mucosa.[22] This treatment has significantly improved over the past decade, notably through the use of immunomodulator and biologic drugs. However, there is a discrepancy between measures of gut inflammation and the extent and severity of patients' symptoms and overall quality-of-life (QoL).[23]

In large cohorts of patients with IBD, 60% report abdominal pain, substantially more than the 25% prevalence observed in samples of the general population.[24,25] In this patient group, abdominal pain presents a common, disabling, unresolved problem, affecting patients' QoL and psychological well-being. This means disease-targeted treatment alone may not be sufficient for IBD, and that additional management strategies aimed at improving QoL, and particularly chronic pain, are needed.[26,27]

Multimodal chronic pain management approaches are increasingly considering cannabis as an option for patients who are refractory to standard care, with The National Academies of Science, Engineering and Medicine (NASEM) 2017 report stating that there is "conclusive or substantial" evidence that cannabinoids are an effective treatment for chronic pain in adults.[28]

Nascent evidence suggests cannabis may also be beneficial in improving anxiety and sleep[29]; QoL factors linked to the psychological distress commonly experienced by patients with IBD.[30]

Taken together, this provides the rationale for researching the role of the ECS in maintaining gastrointestinal (GI) health and investigating medical cannabis as a potential adjunctive treatment option for patients with IBD.

The ECS and IBD

All components of the ECS are present in the GI tract.[31]

CB1 receptors are primarily present in enteric cholinergic neurones, where they inhibit neuronal hyperactivity, thus alleviating strong bowel contractions and secretion.[32] CB1 receptors are also expressed in enterocytes where they are most likely involved in the regulation of mucosal permeability and wound healing.[33]

CB2 receptors, instead, are mainly found in B and T cells as well as macrophages, where they contribute to the role of the ECS in the maintenance of immune tolerance.[34]

Blockade of MGL (2-AG degrading enzyme) has been shown to reduce experimentally induced colitis, suggesting that increased ECS activity may help to reduce intestinal inflammation.[35]

ECS components are also abundantly present in the brain. Central application of CB receptor agonists has been shown to improve inflammation in a mouse model of colitis, consistent with cannabinoid-mediated modulation of the gut-brain axis.[36]

Genetic deletion of an enzyme involved in AEA synthesis in intestinal epithelial cells was found to alter the composition of the gut microbiota, supporting a physiological ECS-microbiota relationship.[37]

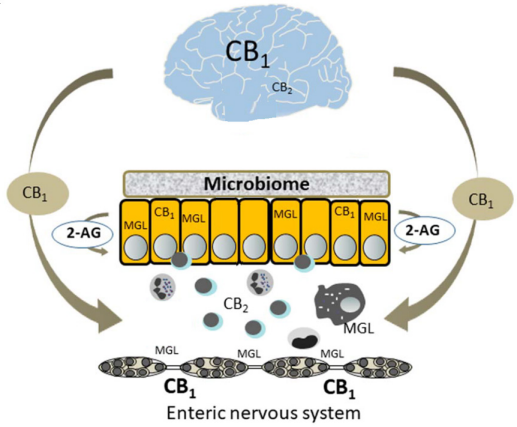


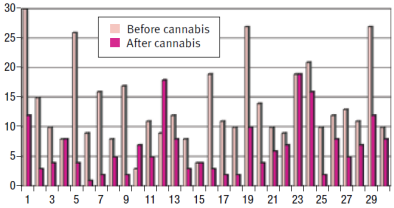
Figure 6 – Potential mechanisms underlying beneficial effects of cannabis/cannabinoids in IBD[38]

Medical cannabis for the management of IBD

Survey data has revealed that taking cannabis for medical purposes is common among patients suffering with IBD, with self-reported efficacy in reducing abdominal pain, abdominal cramping, joint pain, diarrhoea and improving appetite.[39,40,41,42]

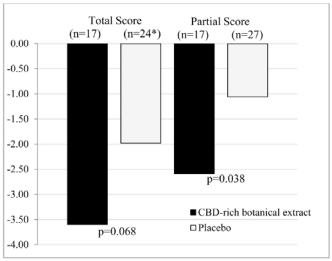
An initial 2011 observational study in Crohn's disease found that 70% of patients' symptoms improved significantly after treatment with cannabis, with reduced need for surgery and other medications.[43]

Figure 7 – Harvey-Bradshaw index score (assessment of Crohn's disease activity) before and after cannabis use in each of the 30 patients in the study.[43]



Subsequent randomised-controlled trials have shown improved disease activity and QoL scores with cannabis compared to placebo in both ulcerative colitis and Crohn's disease.[44,45,46,47,48] A reduction in laboratory parameters of inflammation is, however, yet to be reported.[48] One study showed that low-dose CBD is not effective in the treatment of Crohn's disease.[49]

Figure 8 – Mayo scores (assessment of ulcerative colitis disease activity): change from baseline to final visit following treatment with either placebo or a CBD-rich botanical extract. In the placebo group, only 24 patients have a total Mayo score as 3 did not have an end of treatment endoscopy performed.[45]



A 2020 review of the evidence commented that although a reduction of independent anti-inflammatory markers has so far not been demonstrated, several studies show a significant improvement in QoL in patients with IBD after cannabis use. Cannabinoids could therefore be a potentially valuable tool as an add-on treatment when symptoms such as abdominal pain remain a problem despite good control of the inflammation.[38]

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.[50] 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.[51]

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.[52]

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.[53] CB1 receptors are not expressed in the brainstem, which may explain the lack of cannabis-related fatalities due to respiratory depression.[54]

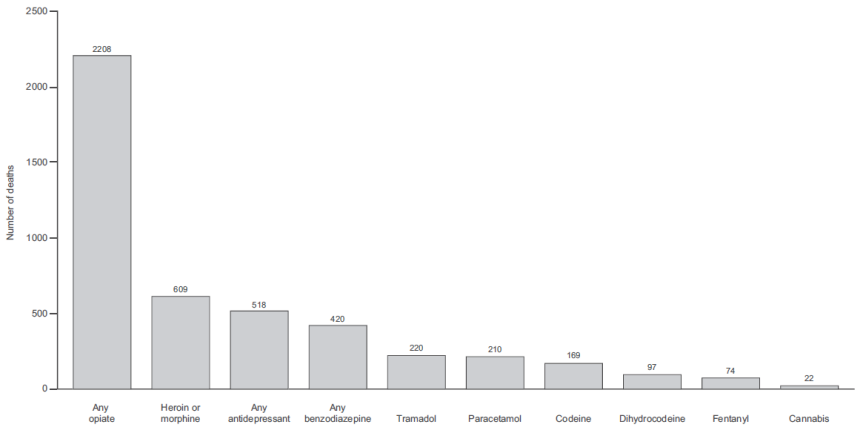


Figure 9 – Number of deaths related to selected drugs – where the drug was listed on the death certificate – in England and Wales in 2018 [53]

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:
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