GROW
PHARMA

# Medical cannabis and rheumatoid conditions

An introductory overview for healthcare professionals

## 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

For years, political prohibition and societal stigma slowed both acceptance of cannabis for medicinal purposes and research into its potential benefits. However, globally, as more and more countries are legalising medical cannabis, perceptions are now changing, and research interest has grown exponentially.

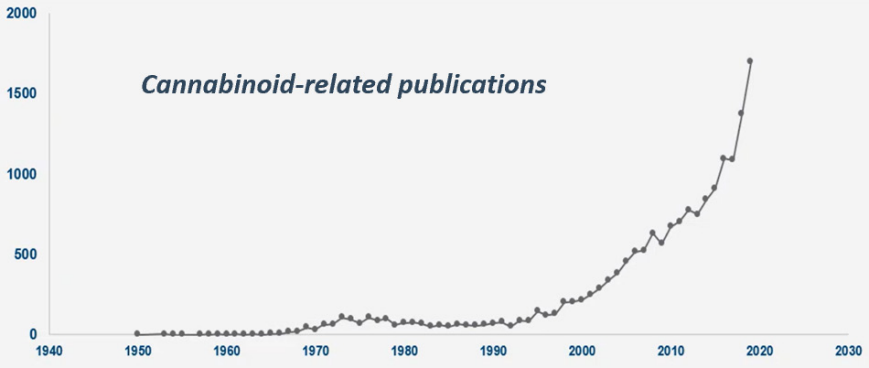


**Figure 1** - Cannabinoid-related publications (accessed at PubMed 31-10-2019)

The UK legalised medical cannabis in November 2018, and currently there are over 15,000 patients using it to relieve the symptoms of their condition, most commonly chronic pain. This is predominantly through specialist clinics that have been set up to facilitate patient access to unlicensed cannabinoid medicines.

JAMA The Journal of the American Medical Association

The National Academies of SCIENCES ENGINEERING MEDICINE

A landmark 2015 systematic review published in JAMA[1] 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 concluded that there is "moderate" quality evidence to support the use of CBMPs for the treatment of chronic pain. The National Academies of Science, Engineering and Medicine (NASEM) 2017 report[2] (US equivalent of the Royal Society in the UK) went further, stating that there is "conclusive or substantial" evidence that cannabinoids are an effective treatment for chronic pain in adults.

## The Endocannabinoid System (ECS)

The ECS consists of cannabinoid receptors, endocannabinoids, and their metabolic enzymes.[3]

Cannabinoids are produced endogenously by all vertebrates, with anandamide (AEA) and 2-arachidonoylglycerol (2-AG) being the most well-known.[4] 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.[5]

The ECS regulates many physiological processes including inflammation and pain perception, immunity, neuropathy, and metabolism.[3]

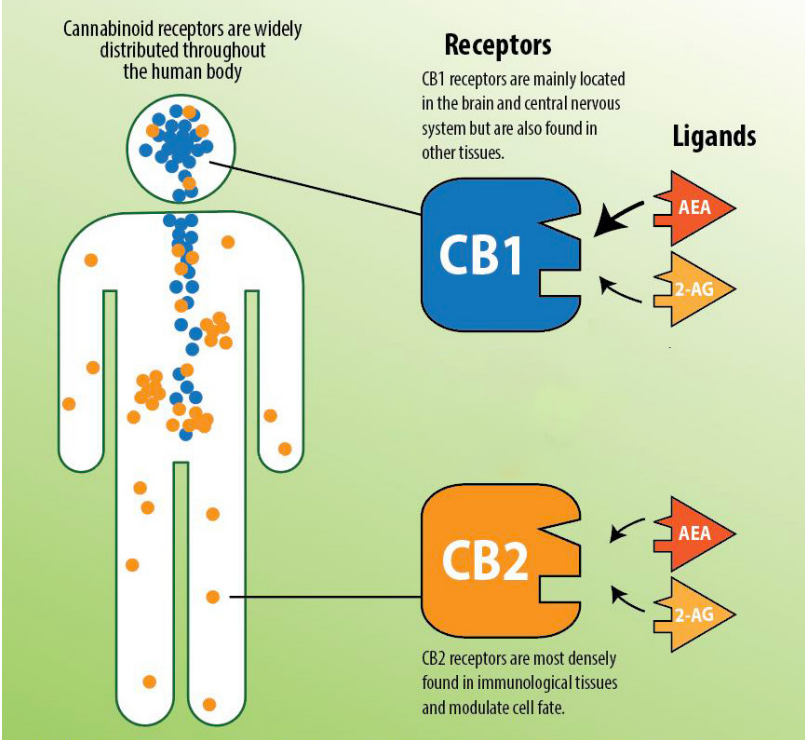


**Figure 2** – The Endocannabinoid System (ECS)[3]

## 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.[6] Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant, most studied and believed to be the most important clinically.[7]

THC produces psychoactive and other physiological effects – such as on pain and appetite – through its partial agonism of CB1 and CB2 receptors.[8]

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$_{1A}$.[9,10,11]

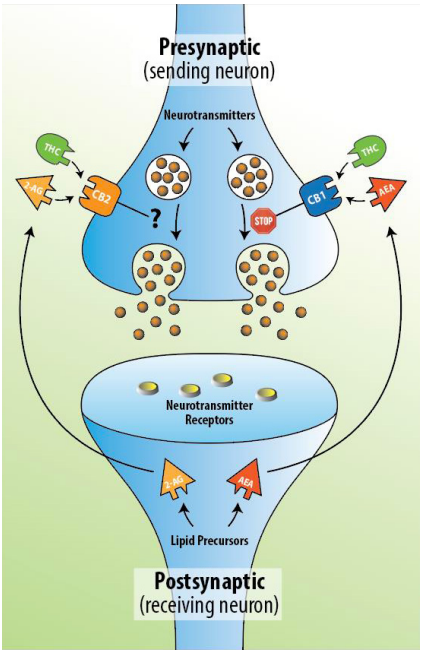


**Figure 3 –** Phytocannabinoid interactions at the synapse[5]

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).[12]

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.[13]

# Medical cannabis for the management of rheumatoid conditions

## Fibromyalgia (FM)

As a chronic pain syndrome with a relative lack of suitable management options, FM is a natural candidate for investigating the potential efficacy of CBMPs. A number of recent studies are outlined in *Table 1* below:

**Table 1** – *Recent studies conducted on the use of cannabis for the treatment of fibromyalgia*

| Study | Interventions studied (ratios represent THC:CBD content) | Design | Results |
|---|---|---|---|
| Van de Donk, 2018 [14] | 22:1, 1:18, 6:8, placebo | Randomised, placebo-controlled, 4-way crossover. 20 patients. | Varieties containing high THC (22:1, 6:8) increased the pressure pain threshold vs placebo in patients with FM |
| Yassin et al, 2019 [15] | Medical cannabis therapy (MCT) – 1:4 (THC < 5%); standardised analgesic therapy (SAT) – 4.5mg oxycodone bd, 2.5mg naloxone hydrochloride bd and duloxetine 30mg od | Observational, crossover, single-centre. 31 patients. 6 months. | Supplementation of SAT with MCT alleviated pain in FM patients suffering from low back pain |
| Giorgi et al, 2020 [16] | 22:1, 6:8 | Prospective, observational. 102 patients. 6 months. | Significant improvements (≥30% vs baseline) in sleep and FM scores were observed in 44% and 33% of patients, respectively. 47% reduced or suspended concomitant analgesic use. |

Table 1 continued

| Study | Interventions studied (ratios represent THC:CBD content) | Design | Results |
|---|---|---|---|
| Chaves et al, 2020 [17] | THC-rich cannabis oil (initial dose of 1.22mg THC and 0.02mg CBD), placebo | Randomised, placebo-controlled. 17 patients. 8 weeks. | THC-rich cannabis oil reduced pain and improved quality-of-life measures vs baseline and vs placebo in patients with FM |
| Sagy et al, 2020 [18] | Cannabis strains containing different THC:CBD ratios | Prospective, observational. 367 patients. 6 months. | FM patients reported lower pain and improved quality of life after 6 months. 22% stopped or reduced their opioid dosage. |
| Mazza et al, 2021 [19] | Cannabis strains containing different THC:CBD ratios | Retrospective, open-label case series. 38 patients. Follow-up at 1–12 months. | FM patients reported lower pain scores at follow-up. 49% experienced non-serious AEs, most commonly mental confusion, dizziness, and nausea. |

A 2021 review of the evidence[20] concluded that the use of CBMPs carries limited side effects and can improve some common and debilitating symptoms associated with FM, thus making it an "adequate potential treatment option when other treatment lines have been exhausted". It goes on to comment that further research in this area should aim to assess long-term efficacy, dependence, adverse events (AEs), and optimal THC:CBD ratio.

## Rheumatoid arthritis (RA) and osteoarthritis (OA)

The ECS was only discovered in the 1990s[21,22], so there is still plenty we do not know about the mechanisms of action of CBMPs. However, in addition to the pain-relieving effects explored in the FM section, there is increasing evidence supporting the anti-inflammatory actions of cannabinoids, and this has potential implications in rheumatoid conditions[23,24].

| Condition | Potential cannabinoid action |
|---|---|
| Rheumatoid arthritis (RA) | • Reduction of cytokine production by RA fibroblasts [25]<br>• Reduction of matrix metalloproteinases (MMPs) release from fibroblast-like synovial cells [25,26]<br>• Reduction of cartilage extracellular matrix (ECM) breakdown [27]<br>• Pain relief [28] |
| Osteoarthritis (OA) | • Decreased activity of MMPs and nitric oxide production in OA chondrocytes [29,30]<br>• Inducement of chondrocyte apoptosis [31] |
| Fibromyalgia (FM) | • **Pain relief [14,15,16,17,18,19]** |

**Table 2** – *Possible mechanisms of cannabinoid action in different rheumatoid conditions*

Clinical trials of CBMPs in patients with RA or OA are however currently lacking, with a notable exception being a study from 2006[28]. In this double blind randomised-controlled trial (RCT), 58 patients suffering from pain related to RA received either a balanced THC:CBD product (nabiximols) or placebo for 5 weeks. Nabiximols was found to produce statistically significant improvements in pain on movement, pain at rest, quality of sleep, and disease activity compared to placebo.

More recently, a survey of 319 rheumatology clinic outpatients taking cannabis reported improved pain and quality of sleep, however only 4% were taking cannabis for inflammatory issues (the majority were taking it for FM), hence providing limited information regarding its potential effectiveness in RA or OA.[32]

## Safety considerations

Patients receiving CBMPs commonly experience transient AEs, however the incidence of serious AEs is generally not significantly different compared with control individuals.[33] 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.[34]

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.[35]

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.[36] CB1 receptors are not expressed in the brainstem, which may explain the lack of cannabis-related fatalities due to respiratory depression.[37]

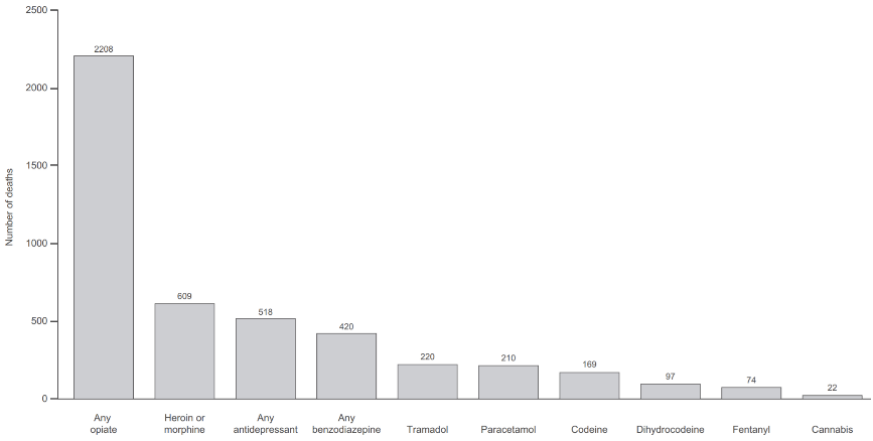


**Figure 4** – Number of deaths related to selected drugs – where the drug was listed on the death certificate – in England and Wales in 2018[36]

The oromucosal spray Sativex contains both THC and CBD, so although it is licensed for multiple sclerosis, 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 4th January 2023)

## Further reading

Cannabinoids for the management of RA, OA and other rheumatoid conditions including systemic sclerosis – literature reviews:

Katz-Talmor.D, Katz.I, Porat-Katz.B et al. Cannabinoids for the treatment of rheumatic diseases – where do we stand? (2018). Nature Reviews Rheumatology 14:488–498

Sarzi-Puttini.P, Ablin.J, Trabelsi.A et al. Cannabinoids in the treatment of rheumatic diseases: pros and cons (2019). Autoimmun Rev 18(12):102409 Epub 2019

Medical cannabis for fibromyalgia – literature review:

Khurshid.H, Qureshi.I, Jahan.N et al. A systematic review of fibromyalgia and recent advancements in treatment: is medicinal cannabis a new hope? (2021) Cureus 13(8):e17332

A recent study investigating the anti-inflammatory properties of CBD and its implications for the management of RA:

Lowin.T, Tingting.R, Zurmahr.J et al. Cannabidiol (CBD): a killer for inflammatory rheumatoid arthritis synovial fibroblasts (2020). Cell Death and Disease 1:714

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