GROW
PHARMA

Medical cannabis for the management of cancer symptoms and treatment-induced side effects

An introductory overview for healthcare professionals

Introduction to Grow Pharma

Grow Pharma (www.grow-pharma.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) – for multiple sclerosis (MS)
- Epidiolex (cannabidiol) – for rare forms of epilepsy
- Nabilone (synthetic THC) – for chemotherapy-induced nausea and vomiting (CINV)

Aside from nabilone for CINV, there are currently no other licensed cannabis medicines indicated for the management of cancer symptoms or treatment-induced side effects. 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 managing symptoms and conditions which may benefit from CBMPs. 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]

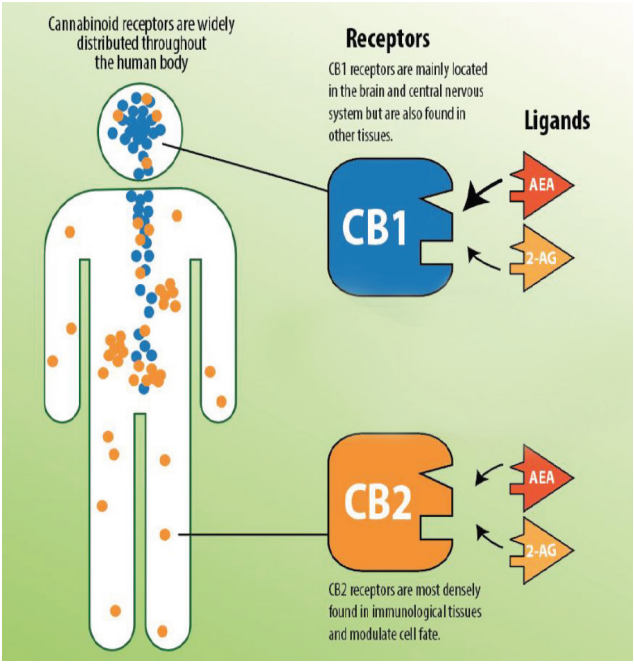

Figure 2 – The Endocannabinoid System (ECS)[6]

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]

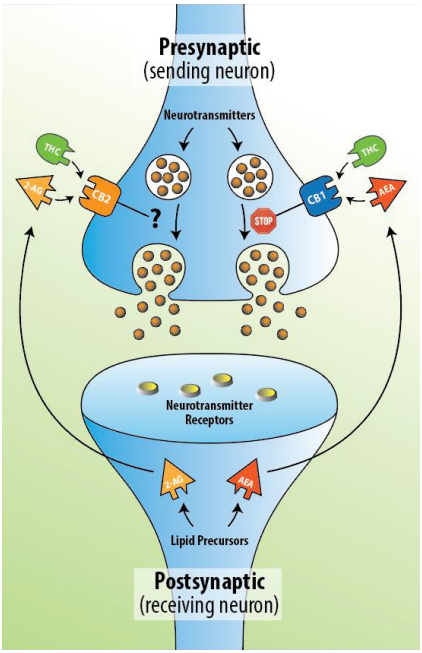

Figure 3 – Phytocannabinoid interactions at the synapse[6]

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]

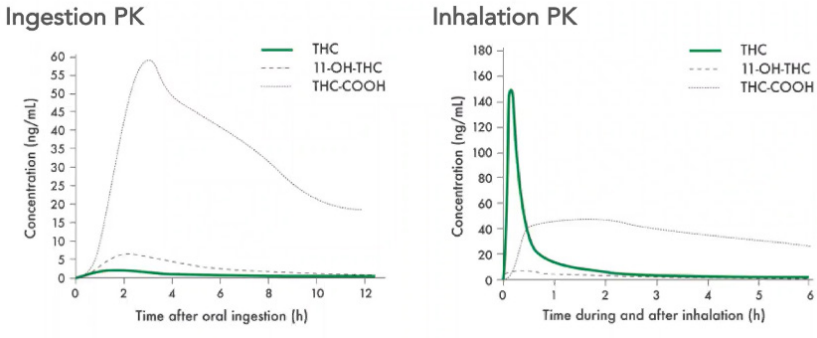

Figure 4 – *The pharmacokinetics associated with different routes of administration*[20]

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] The optimal THC:CBD ratio is also likely to be determined by the nature of the symptoms being managed.

Nabilone for CINV is typically administered twice daily (maximum daily dosage is 6mg), 1–3 hours before chemotherapy.

No standardised dosing regimen currently exists for treating other cancer-related symptoms with CBMPs. However, when introducing THC, typically a 'start low, go slow' approach is adopted, whereby the dose of THC is gradually increased until a balance between satisfactory symptom control and minimal adverse effects is reached.[18]

In an advanced cancer/palliative care setting, it is likely that the speed of THC escalation may be greater due to the shifted risk-benefit paradigm.

Typically, clinicians would consider starting the first dose of THC in the evening in order to limit potential issues with workplace functioning and driving and to aid sleep.[19] However, the former reasons may not be as relevant in a palliative care setting.

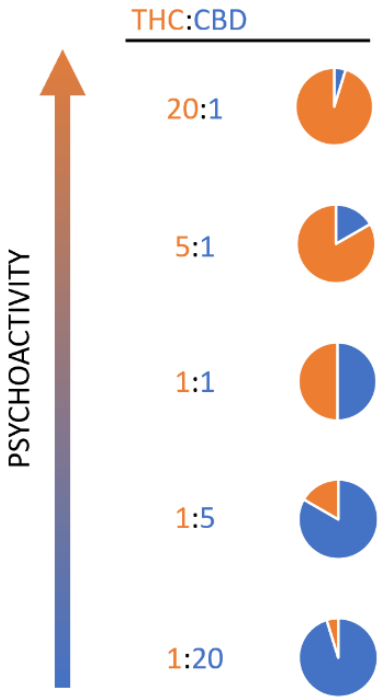

Figure 5 – Depiction of different THC:CBD ratios and their levels of psychoactivity.

Medical cannabis for the management of cancer symptoms and treatment-induced side effects

The goal of medical cannabis treatment in an oncology context is to improve a cancer patient's overall quality-of-life (QoL). In particular, there is evidence to support the use of medical cannabis for improving pain, anxiety, sleep, CINV, and anorexia/cachexia in patients with cancer. This section explores each of these in turn.

Cancer 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] 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]

Most of the studies conducted thus far with CBMPs have focused on managing chronic non-cancer pain. However, cancer pain is fast emerging as a key area of interest in the field of cannabinoid research.

A 2010 randomised controlled trial (RCT) found that a THC:CBD balanced extract (but not a THC-only extract) was efficacious in reducing pain compared to placebo in cancer patients whose pain was not fully relieved by strong opioids.[24]

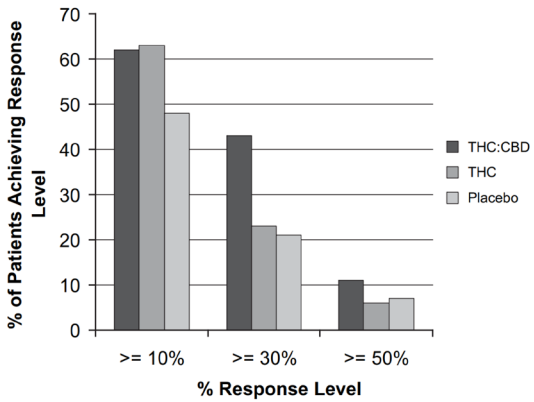

Figure 6 – Percentage of patients achieving a response level in Numerical Ratin Scale (NRS) pain score vs basline. A reduction in pain NRS of at least 30% is considered to represent a clinically important difference.[24]

A more recent RCT found that a balanced THC:CBD extract reduced pain and improved QoL, however the former was not statistically significant (p = 0.09). Interestingly, the cannabinoid treatment was found to be more effective in US patients (who were taking lower doses of opioids at baseline) than in patients from the rest of the world. This led the authors to suggest that CBMPs could be particularly useful in patients with advanced cancer who receive a lower opioid dose, such as individuals with early intolerance to opioid therapy.[25]

Several large observational trials have also reported reduced pain, alongside improvements in other QoL measures, among cancer patients who started taking medical cannabis.[26,27,28]

Most recently, studies have investigated the potential for CBMPs to have opioid sparing effects in cancer patients. A 2020 chart review of 232 cancer patients found that in a palliative care patient cohort, CBMPs improved symptoms and prevented opioid dose escalation (Fig. 7).[29]

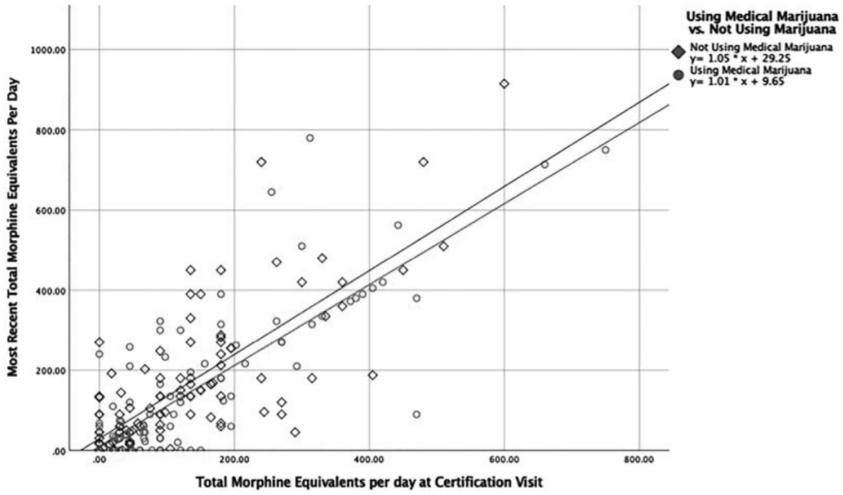

Figure 7 – Grouped scatter of most recent total morphine equivalent dose per day by total morphine equivalent dose per day at baseline.[29]

Similarly, a 2021 study concluded that addition of medical cannabis to standard oncology care was well-tolerated and led to improved pain control and lower opioid requirements.[30]

Sleep and anxiety

The ECS has been found to be a modulator of anxiety and mood. At low doses, THC activates CB1 receptors in glutamatergic terminals, having an anxiolytic effect. At high doses, THC activates CB1 receptors in GAB-Aergic neurones, having an anxiogenic effect.[31] The anxiolytic effects of CBD are thought to be mediated by activation of 5-HT_{1A} receptors.[32]

With regards to sleep, there is abundant anecdotal survey evidence for the soporific effect of cannabis, with sufferers of a range of conditions reporting that it assists in the management of insomnia.[33,34] Additionally, somnolence is a commonly listed adverse event (AE) in clinical trials involving CBMPs. However, THC at high doses has the potential to cause sleep disturbances due to its anxiogenic effects.[34]

There is emerging evidence supporting the use of CBD in anxiety disorders[35,36] and THC-predominant products for insomnia[37]. To date, however, there have not been any trials investigating anxiety or sleep as a primary outcome measure in cancer patients. Instead, the evidence in an oncology context has thus far come from observational studies including sleep and anxiety end-points as part of a general QoL assessment.

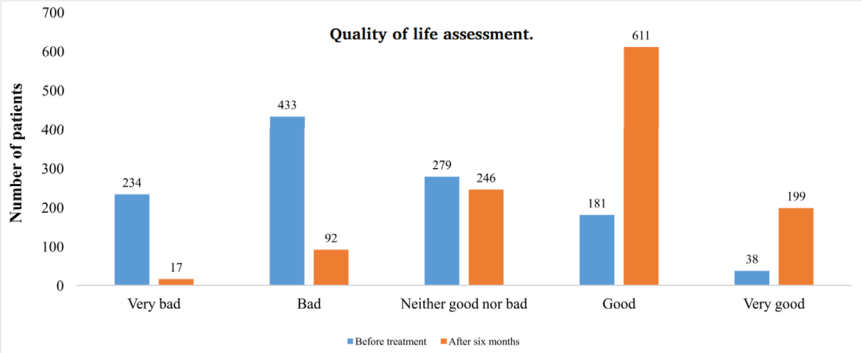

Figure 8 – Quality of life assessment. Quality of life was assessed prior to and six months after initiation of cannabis treatment.[27]

A large retrospective study of 3,845 Israeli cancer patients taking medical cannabis for palliative care reported that 51% exhibited a significant improvement in their condition after 6 months relative to baseline, with 70% reporting at least "good" QoL compared to 19% at baseline.[27]

A 2013 observational study of 211 cancer patients taking medical cannabis for 6–8 weeks reported improvements in pain, sleep, and mood. Among the patients who used antidepressants or anti-anxiety drugs at baseline, 33% had discontinued them at follow-up.[26]

Most recently, a prospective study of 324 cancer patients taking medical cannabis revealed significant improvements after 6-months in most outcome measures, including anxiety, sleep disturbances, depression, and pain, with the total symptom burden declining from baseline by a median of 18%.[28]

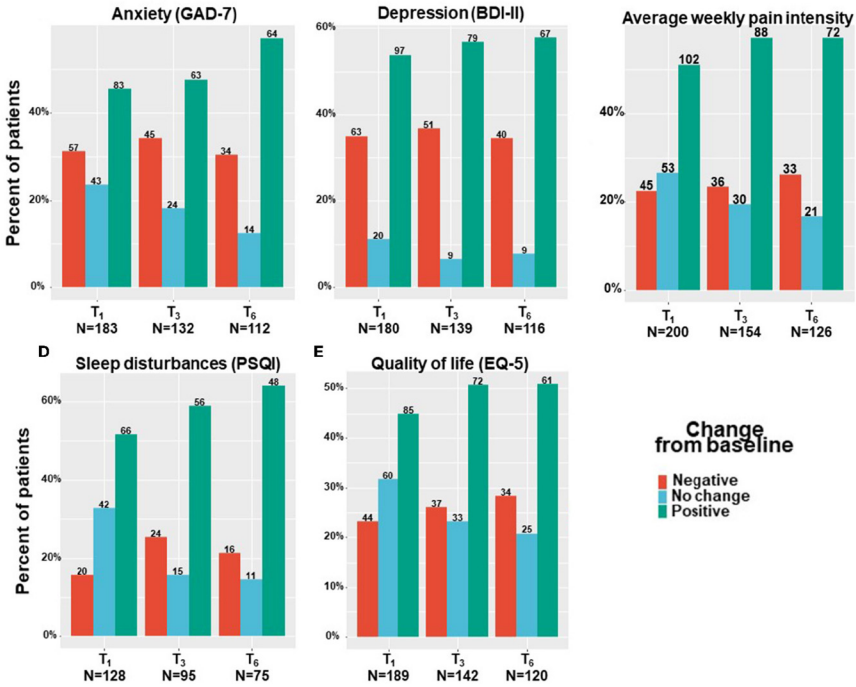

Figure 9 – Cancer comorbid symptoms change from baseline. T1, 1-month Follow-Up; T3, 3-month Follow-Up; T6, 6-month Follow-Up. GAD-7, general anxiety disorder; BDI, Beck depression inventory; PCS, pain catastrophizing scale; PSQI, Pittsburgh sleep quality index; EQ-5, Euro-QoL questionnaire. "Negative" indicates patients that reported on higher comorbid symptoms at a follow-up compared to baseline; "Positive" indicates patients that reported on lower comorbid symptoms at a follow-up compared to baseline; "No change" indicates patients that reported on the same comorbid symptoms at a follow-up compared to baseline. Numbers of patients are based on patients that reported fully on the measures at baseline and at the corresponding follow-up time point.[28]

CINV

The antiemetic effects of the ECS appear to be produced by a multi-step process in which CB1 ligands act as retrograde synaptic messengers. Consistent with this, CB1 receptor antagonists have been shown to induce vomiting in animals, while THC – a partial agonist of CB1 receptors – exhibits anti-emetic effects.[38]

Nabilone (synthetic THC) is licensed in the UK for CINV in adults. It is also approved by the Food and Drug Administration (FDA) in the US for CINV in cancer patients who fail to respond adequately to conventional antiemetic treatments.

Nabilone is typically given 1–2mg b.d, with the first dosage administered 1–3 hours before the start of chemotherapy. The maximum recommended daily dosage is 6mg.

Most of the original studies supporting the use of nabilone in CINV were conducted in the 1970s and 1980s, leading to FDA approval in 1985. For example, a double-blind, randomised, crossover trial published in 1981 found that nabilone was superior to prochlorperazine in reducing nausea and vomiting associated with chemotherapy.[39]

A 2001 review summarising the active- and placebo-controlled studies conducted with CBMPs for managing CINV highlighted a preference for cannabinoids.[40]

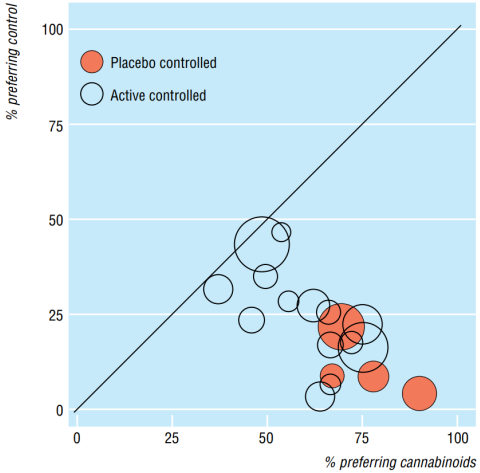

Figure 10 – Percentages of patients preferring cannabinoids or control for future chemotherapy. Each symbol represents one trial. Symbol sizes are proportional to trial sizes. The solid line represents equality.[40]

Anorexia/cachexia

The ability of cannabinoids to reduce CINV is one method to counteract malnourishment associated with oncology treatment. Dronabinol (synthetic THC) has been utilised in AIDS patients since 1985 when it was first approved by the FDA in the US to combat anorexia associated with AIDS. Interest has subsequently carried over to the field of oncology to determine whether cancer patients could achieve similar enhancements in appetite. However, despite cannabis having relatively established appetite stimulating effects in healthy individuals – and increased appetite being a common AE in CBMP clinical trials – data gathered thus far in cancer patients has overall yielded mixed results.

A 2002 study found that megestrol acetate provided superior anorexia palliation among advanced cancer patients compared to dronabinol, while a combination of dronabinol and megestrol acetate did not appear to confer additional benefit compared to megestrol acetate alone.[41] A more recent RCT from 2006 found no difference in cancer patients' appetite or QoL between a THC:CBD extract, THC, and placebo.[42] It is possible that the results of these studies could be due to the use of low cannabinoid doses and synthetic isolates (rather than whole-plant preparations), but further research is needed to verify this.

More promisingly, a preliminary trial published in 2019 found that taking THC-rich capsules for 6-months led to a weight gain of more than 10% in three of the six patients who completed the study period.[43]

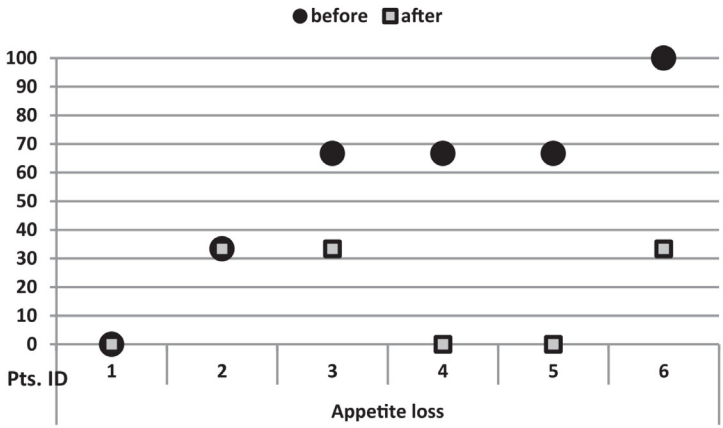

Figure 11 – EORTC QLQ-C30 appetitive loss subscale among the 6 patients who completed the cannabis treatment (EORTC QLQ-C30, European Organization of Research and Treatment of Cancer Quality of Life Questionnaires).[43]

Anticancer effects of cannabinoids

As previously outlined, the goal of medical cannabis treatment in an oncology context is to improve a patient's QoL. However, there is an emerging body of preclinical research that suggests cannabinoid compounds could also have anticancer effects at multiple levels of tumour progression via different signal transduction mechanisms.[44]

A recent review by Hinz & Ramer states that there is "considerable evidence for cannabinoid-mediated inhibition of tumour cell proliferation, tumour invasion and metastasis, angiogenesis and chemoresistance, as well as induction of apoptosis and autophagy."[44]

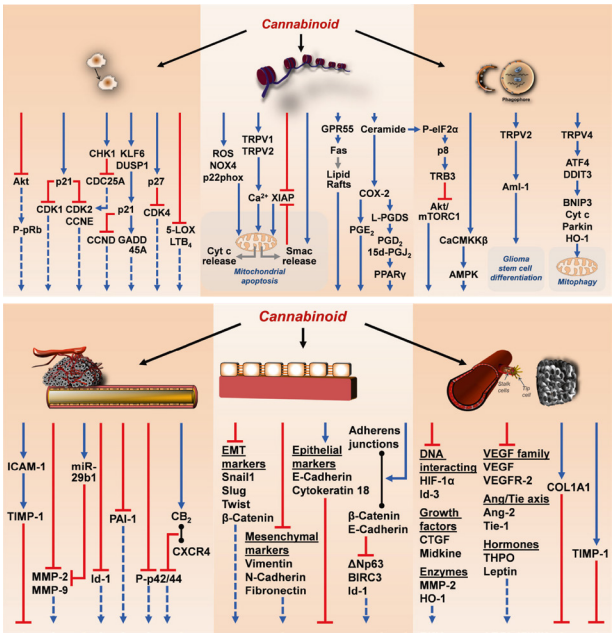

Figure 12 – Mechanisms of antiproliferative, proapoptotic and proautophagic, anti-invasive, antimetastatic, anti-epithelial-to-mesenchymal transition and antiangiogenic effects of cannabinoids on cancer cells.[44]

A 2019 study investigating various combinations of cannabis extracts and their effects on different cell lines found that variable responses were obtained depending on the cancer type and content of the cannabis extract. Interestingly, two extracts containing equal amounts of THC, but varying levels of other cannabinoids, had different outcomes in terms of cell death, suggesting that the interplay of all the different cannabinoids present may be the true determining factor of an extract's effectiveness rather than the amount of THC alone. On this basis, the authors recommended whole extract cannabinoid therapy over pure (isolate/synthetic) THC.[45]

Preclinical studies have also shown that cannabinoids could be potential combination partners for established chemotherapeutic agents such as vinca alkaloids, temozolomide and cisplatin. The mechanisms of these synergies are, however, not yet fully understood.[46]

Despite the encouraging preclinical evidence to date, there is a dearth of clinical trials, aside from a phase 1b study published in 2019 which found that patients taking a balanced THC:CBD extract in combination with temozolomide had higher survival rates after 1 year than those taking temozolomide alone.[47]

There have also been a handful of isolated case studies in the literature. A case report from 2019 concluded that self-administration of CBD oil may have had a role in the partial tumour response seen in an 81-year-old man with histologically proven adenocarcinoma of the lung.[48]

Similarly, a 2021 BMJ case report suggested that self-administration of a THC:CBD oil may have had a role in the tumour regression observed in an 80-year-old-woman with lung cancer.[49]

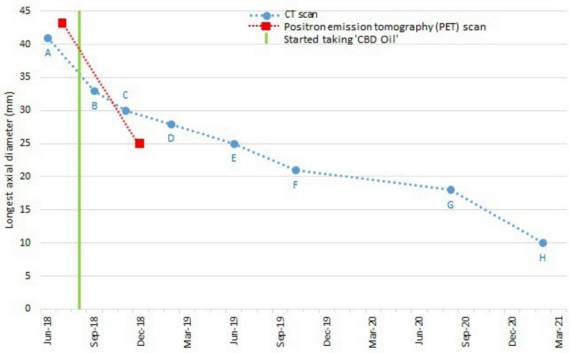

Figure 13 – Tumour shrinkage over a 4-year period as measure by regular CT scans.[49]

In a recent comprehensive review of the literature, Hinz & Ramer conclude by cautioning that despite the promising findings thus far, "research into the efficacy, dosage and drug safety of cannabinoids in tumour therapy still has a long way to go, especially with regard to clinical trials to be conducted, through which alone the benefits and advantages for cancer patients but also possible risks can be defined".[44]

Further reading

General:

Sexton.M et al. The management of cancer symptoms and treatment-induced side effects with cannabis or cannabinoids (2021). J Natl Cancer Inst Monogr *58:86–98*

Cancer pain:

Boland.E et al. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis (2020). *BMJ Supportive and Palliative Care* 10:14–24

Chung.M et al. Update on cannabis and cannabinoids for cancer pain (2020). *Current Opinion in Anaesthesiology* 33:825–831

CINV:

Tramer.M et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review (2001). *BMJ* 323:16–21

Ware.M et al. A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting (2008). *Therapeutics and Clinical Risk Management* 4:99–107

Anticancer effects:

Hinz.B & Ramer.R. Cannabinoids as anticancer drugs: current status of preclinical research (2022). *Br J Cancer* 127 1–13

Safety considerations

Patients receiving CBMPs commonly experience transient 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]

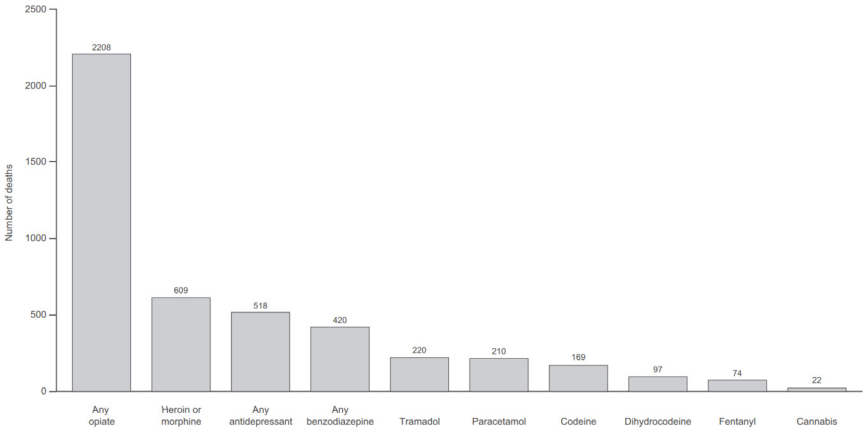

Figure 14 – Number of deaths related to selected drugs – where the drug was listed on the death certificate – in England and Wales in 2018.[53]

Sativex contains both THC and CBD, so although it is licensed for 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 5 October 2022)

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