THE USE OF CANNABIS-BASED MEDICINAL PRODUCTS (CBMPS) IN PAIN

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The use of Cannabis-based medicinal products (CBMPs) in pain

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Glossary

**AEA**: anandamide, the first identified endogenous (made in our body) cannabinoid

**Bioavailability**: the ability of a medicine to get into our bloodstream

**CB1**: the first identified cannabinoid receptor

**CB2**: the second identified cannabinoid receptor

**CBD**: cannabidiol, phytocannabinoid that does not cause a high

**CBMPs**: Cannabis-based medicinal products

**Clinical trial**: an investigation of the effectiveness of a medicine, usually in comparison to placebo and/or standard care (controlled)

**DDI**: drug-drug interactions, when one medicine interferes with the action of another medicine

**Dronabinol**: synthetic THC, licensed in the US

**Epidiolex**: pure CBD produced as a medicine licensed in epilepsy in the US

**Nabilone**: a structural analogue of THC, licensed in the US and UK

**Primary endpoint**: the main outcome of a clinical trial the investigators hypothesise will be positively changed by a medicine (usually a pain rating in this subject area)

**RCT**: randomised controlled trial, the gold standard of clinical research

**Sativex**: CBD:THC in a 1:1 ratio licensed internationally for spasticity in MS, also known as nabiximols

**Secondary endpoint**: additional supportive or important outcomes of a clinical trial the investigators think will be positively changed by a medicine (often includes quality of life scores)

**Sublingually**: a medicine taken under the tongue, common for CBMPs

**THC**: Δ9-tetrahydrocannabinol, an abundant metabolite of the Cannabis plant that causes the ‘high’
Introduction

UK Legislative context

In the summer of 2018, Home Secretary Sajid Javid announced the UK would be making medicinal cannabis available after receiving advice from Professor Dame Sally Davies, Chief Medical Officer for England and Chief Medical Adviser to the UK government, that cannabis-based medicinal products should be moved out of a Schedule 1 classification where compounds have no medicinal value. On November 1, 2018, cannabis-based medicinal products (CBMPs) were rescheduled to allow lawful prescription as unlicensed medicines by specialist doctors (consultants). The Home Office definition of a CBMP is as follows:

- the product is or contains cannabis, cannabis resin, cannabinol or cannabinol derivatives
- the product must be produced for medicinal use in humans
- it must be a product that is regulated as a medicinal product or an ingredient of a medicinal product

Current guidelines for CBMPs in Pain

After the change in law, the UK Government asked for interim guidance on the medicinal use of CBMPs. One report was jointly produced by the Royal College of Physicians (RCP), the Royal College of Radiologists (RCR) in liaison with the Faculty of Pain Medicine of the Royal College of Anaesthetists. The summary of their research was that ‘There is limited research available from which to create guidance on the effect of CBMP on pain in palliative care patients, including those with cancer. Studies show mixed results or statistically significant results of uncertain clinical significance. In view of this and the adverse effects associated with CBMP, their place in the treatment of pain in palliative care patients is unclear and not recommended in routine clinical practice. There is no robust evidence for the use of CBMP in chronic pain and their use is not recommended.’

The NHS website states ‘There is some evidence medical cannabis can help certain types of pain, though this evidence is not yet strong enough to recommend it for pain relief.’

For these reasons, it is likely to be extremely challenging to access CBMPs for pain management under the NHS.

The National Institute for Health and Care Excellence (NICE) is currently defining the final guidelines which will be published no later than October 2019. Chronic pain has been listed as a key area that will be covered in their research. Within this, specific considerations will be given to young and older people, those with learning disability or mental health problems, and pregnant or breastfeeding women.

2 https://www.rcplondon.ac.uk/projects/outputs/recommendations-cannabis-based-products-medicinal-use
3 https://www.nhs.uk/conditions/medical-cannabis/
4 https://www.nice.org.uk/guidance/ind10124
Introduction to cannabis and cannabinoids

The *Cannabis* sativa plant produces hundreds of chemicals which are concentrated in structures called glandular trichomes on the flower of the plant. These chemicals are known as cannabinoids; or more specifically, phytocannabinoids, because they come from the plant. Usually, the most abundant phytocannabinoid found in cannabis flowers is Δ⁹-tetrahydrocannabinol (THC). THC normally comprises about 10-18% of the chemicals depending on the cannabis plant strain. This is the psychotropic (mood altering) chemical that produces the responses in our body that you might be familiar with; euphoria (feeling high), wanting to eat, effects on memory and analgesia (the ability to relieve pain). Normally, the next most abundant cannabinoid is cannabidiol (CBD). CBD is the chemical that makes you feel mellow and reduces anxiety, and is evidenced to be useful in a wide range of disorders such as epilepsy, schizophrenia, post-traumatic stress disorder (PTSD) and stroke.

The definition of a cannabinoid can involve chemicals other than those phytocannabinoids that come from the plant, and can include chemicals that are similar to phytocannabinoids and that bind to the cannabinoid receptors in our body. This includes synthetic cannabinoids that are manufactured artificially (these may be structurally similar or identical to phytocannabinoids or structurally diverse such as street “spice”) and endocannabinoids, chemicals that are produced within our bodies to control a range of processes.

Introduction to the endocannabinoid system

Initial scientific thinking was that cannabis had a non-specific effect on the function of cells in our body. However, approximately 30 years ago, it was discovered that there are particular proteins (termed receptors) on the surface of our cells that recognise and bind cannabinoids, resulting in a change in the function of these proteins, leading to the effects we recognise when people consume *Cannabis* preparations. The first receptor discovered was called the cannabinoid receptor 1 (CB₁). Activation of CB₁ is the way THC brings about most of its biological effects such as euphoria, appetite stimulation and analgesia. The CB₁ receptor is found all over the body, but has particularly high levels across the brain.

The second cannabinoid receptor, called cannabinoid receptor 2 (CB₂) was discovered a couple of years later. It is expressed particularly in cells of the immune system. Levels of this receptor are increased in many tissues, however, when there is damage or infection.

After the discovery of cannabinoid receptors in our body, people began to investigate whether we produce chemicals within our body that bind to these receptors, and quickly discovered a molecular derived from fatty acids called arachidonoyl ethanolamine (also known as anandamide, AEA). AEA is similar to THC in that it can activate both CB₁ and CB₂. A second compound called 2-arachidonoylglycerol (2-AG, also activates CB₁ and CB₂) was also found soon afterwards. These compounds were termed ‘endocannabinoids’ and we now know that these represent two families of endocannabinoids which are formed through independent pathways in our bodies.
The endocannabinoid system is involved in almost every biological function in the body, in the central nervous system but also in all organs; dysregulation of the endocannabinoid system contributes to many disease states including pain.

Currently licensed CBMP medicines

The Home Office definition of a CBMP represents an incredibly broad potential range of products which potentially complicates clinical decision making. We recommend that there are four types of CBMPs for which we have clinical trial evidence:

- CBD only products (such as Epidiolex\(^5\), which is licensed in the US for seizure reduction in epilepsy)
- THC only products (such as nabilone\(^6\) (a molecular similar to THC, licensed in the US and UK) and dronabinol\(^7\) (a synthetic version of THC, licensed in the US), which are licensed for HIV/AIDS induced anorexia and chemotherapy induced nausea and vomiting)
- Products that have a CBD:THC ratio of 1:1 (such as Sativex\(^8\), which is licensed internationally for spasticity in MS. However, it should also be recognised that Sativex also contains other plant products in small quantities.)
- Whole flower products (such as Bedrocan Flos or similar flower products) which can be purchased with specific ratios of THC:CBD according to the patient’s preference.

Evidence exists both in the form of clinical trial data and patient testimonies that all of these products may be useful in the management of pain.

CBMP use in pain management

The use of CBMPs for pain in the UK

The United Patients Alliance (UPA) carried out a survey on UK medicinal Cannabis users in 2018\(^9\). This self-administered questionnaire investigated the extent and range of consumption of cannabis for medicinal purposes and was conducted from July to August 2018\(^10\). The UPA survey found the largest primary reason that patients were using Cannabis was for the relief of pain (10.7%). Arthritis (3.8%), fibromyalgia (3.5%), migraines (3.1%), headaches (2.7%), sciatica (2.5%) and neuropathy (2.5%) were also listed separately as primary reasons for medicinal cannabis use. In total, this suggests that nearly 29% of medicinal cannabis users in the UK do so for the primary relief of pain, or 65% if you combine patients who use CBMPs for pain as the primary and also secondary reason. The other primary reasons for CBMP use in the UK according to the survey were depression, anxiety, insomnia, arthritis, muscle spasms and gut disorders. The 2018 UPA data is in agreement with an older survey from 2005 of 2969 medical Cannabis users where 25% reported using for chronic pain, 21% reported using for arthritis and 19% reported using for neuropathy.

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\(^5\) https://www.epidiolex.com/
\(^6\) https://bnf.nice.org.uk/drug/nabilone.html
\(^7\) http://marinol.com/
\(^8\) http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2033379.pdf
\(^10\) 1750 surveys were returned valid (56% men, 10% under 25, 46% were between 25-44 years, 37% 45-65 years, 7.2% over 65).
Surveys from other countries

A survey carried out in north-eastern US and published in 2017 of 1,513 patients found that 64% were using Cannabis for chronic pain. In Canada, a survey of 628 consumers of Cannabis for therapeutic purposes in 2013 showed 82% were using for pain symptoms. A 2005 survey of 128 patients in Australia found 57% were using medical Cannabis for chronic pain and 35% were using for arthritis.

Together, these surveys show that pain is the main indication for which CBMPs are used in patient groups.

Which cannabis-based products are preferred for pain management?

The UPA survey of medicinal Cannabis users in the UK found similar use of CBD-dominant or THC-dominant products for the treatment of pain as the primary condition (17.4% versus 19.6%). However, more patients appeared to use CBD-dominant products in the treatment of fibromyalgia (16% versus 6%) and arthritis (8% versus 3%).

A survey by the Brightfield Group questioned 2,400 HelloMD medicinal cannabis community members about their medical cannabis use. They found roughly equal numbers of THC-dominant users compared with CBD only users when looking at joint pain, migraines, arthritis of chronic pain.

In a recent self-selected survey of 2490 CBD users in the US, the top three medical conditions reported were chronic pain, arthritis/joint pain, and anxiety. 36% of respondents reported that CBD treated their medical condition “very well by itself”.

Together, this would suggest there is no major preference amongst patients for either THC-dominant or CBD-dominant products in the treatment of pain, although in UK patients, CBD seems to be preferred in the treatment of fibromyalgia and arthritis, although it should be noted that this might also reflect easier access to CBD products in the UK.

Scientific evidence

Animal data and mechanisms of action

The analgesic properties of the cannabis plant have been utilised for centuries in Western and Eastern medicine. However, the understanding of the analgesic effects of cannabis did not begin to be investigated scientifically until the active chemicals of the plant were discovered in the 1960s, and until the cannabinoid receptors were identified in the 1990s. It is worth noting that other phytocannabinoids such as cannabinol (CBN) and cannabichromene (CBC) can also reduce pain in animal models, but these have been less studied than THC or CBD, and have not been explored clinically in patients. From the scientific literature, it has been shown that THC and CBD have different mechanisms of action, and several studies have shown that combined treatment with THC and CBD is more effective than either compound alone.

THC

Δ⁹-tetrahydrocannabinol has been shown to be an effective analgesic in a wide range of animal models of pain since the 1970s. The mechanism of action

11 https://daks2k3a4ib2z.cloudfront.net/595e80a3d32ef41bfa200178/59946dd86c6b200001c5b9cb_CBD_-_HelloMD_Brightfield_Study_-_Expert_Report_-_FINAL.pdf
12 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6043845/
13 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5554313/
of THC in pain mainly involves activation of the CB1 receptor, causing inhibition of the transmission of pain signals. The pain-relieving effects of THC can also involve CB2 activation, for example in inflammatory pain conditions. Additionally interactions occur between cannabinoid and opioid receptors such that THC enhances the pain relieving effects of opioids (a process discussed further in the section on cannabinoids and opioids). THC has also been recently shown in animal studies to enhance the function of glycine receptors which modulate nociception (the perception of pain).

CBD

In animal models, the analgesic effect of CBD is thought to involve the activation of serotonin receptors and ion channels (pores through the cell membrane that allow the transport of ions) called TRPV1 and TRPA1. Like THC, animal studies have shown that some of the analgesic effects of CBD are partly brought about by the ability of CBD to affect glycine receptor function. There does not appear to be a role for CB1 or CB2 activation by CBD in pain models other than the suggestion that CBD can increase the levels of endocannabinoids, and thus indirectly cause cannabinoid receptor activation. Recent animal studies also suggest that CBD enhances the pain-relieving effects of morphine (an opioid).

Clinical Evidence

Summary of published human clinical trials

When the evidence base for the use of CBMPs in patients with pain is considered, a total of 69 clinical studies that have been published between 1975 and 2018 were identified. Only 11 of these studies involved more than 100 patients, the majority being small in size. In general, large patient numbers are required to sufficiently establish the effectiveness of a drug, especially when the outcome measure is subjective. Nine of these larger trials reported positive effects in reducing pain. It is on the basis of multiple studies involving small numbers of patients that the evidence base for CBMPs in pain is largely held to be inadequate. Currently, it is difficult to judge how effective CBMPs are when examining the evidence as a whole because of the different types of CBMPs tested, by different routes of administration, carried out in very different patient populations.

Of the CBMPs tested in randomised controlled clinical trials, only Sativex has been examined in large patient numbers. The data from these trials with Sativex support its licensing for the symptomatic relief of neuropathic pain in multiple sclerosis in Canada.

Effective products in the pain setting

Because different CBMPs have different pharmacological properties, we divided the 69 studies into those that examined the effects of the whole plant, pure CBD, pure THC, or a ratio of THC:CBD (Sativex). In general, trials examining the effects of the whole plant or Sativex were more
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likely to show an improvement in pain ratings (both patient and clinician reported) across a range of pain settings compared to THC alone. Patient testimony to this effect can be found here. There are a limited number of small clinical trials examining the effects of CBD in pain, but all were positive so far.

<table>
<thead>
<tr>
<th>Total number of studies</th>
<th>Whole plant</th>
<th>Sativex</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive trials</td>
<td>14</td>
<td>17</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Negative trials</td>
<td>11 (79%)</td>
<td>11 (65%)</td>
<td>16</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Mixed results</td>
<td>2</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Positive trials with &gt;100 patients</td>
<td>1/1 (100%)</td>
<td>6/8 (75%)</td>
<td>1/2 (50%)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain conditions improved in positive trials</th>
<th>Whole plant</th>
<th>THC</th>
<th>Sativex</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain, neuropathic pain, fibromyalgia, spinal cord injury, diabetic neuropathy, pain associated with Multiple sclerosis, HIV-associated neuropathy</td>
<td>Pain associated with Multiple sclerosis, cancer-related pain, neuropathic pain, diabetic neuropathy, pain due to rheumatoid arthritis</td>
<td>Multiple sclerosis, chest pain, diabetic neuropathy, headache, neuropathic pain, spasticity-related pain, chronic pain, cancer-related pain</td>
<td>Post-operative pain, dysautonomic syndrome, neuropathic pain</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Whole plant</th>
<th>THC</th>
<th>Sativex</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tea, smoked, vapourised, inhaled</td>
<td>Sublingual spray</td>
<td>Oral (tablets, capsules, solution, sublingual spray)</td>
<td>Sublingual spray or oil</td>
<td></td>
</tr>
</tbody>
</table>

A summary of the clinical trials examining the effects of CBMPs in the setting of pain. Positive trials saw a significant change in the primary outcome of the trial (usually a pain rating score) and negative trials did not show a change in the primary outcome. Mixed trials failed to change the primary outcome, but showed positive effects in some of the secondary outcomes.

Secondary (non-pain) endpoints

For many pain studies where a cannabis-based medicine has been tested, it has often been found that there is a significant improvement for patients in secondary measures (other than pain). Some examples of other aspects of chronic pain conditions that have been significantly improved by CBMPs in various clinical trials include anxiety, depression, mood, sleep, daily functioning, social functioning, range of spine motion, global impression of change and quality of life. This data is in agreement with the
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anecdotal evidence and testimonies from CBMP-using pain patients who feel that CBMPs holistically improve many aspects of their condition.

Effective doses and delivery mechanisms in pain disorders

Sativex: Clinical trials that have demonstrated Sativex to be effective in pain settings have used on average between 6 and 12 sprays per day with the guidance of a maximum of 8 sprays per 3 hour period and 24 sprays within a 24 hour period. Each spray of Sativex contains 2.7 mg of THC and 2.5 mg CBD and is delivered sublingually.

THC: Clinical trials that have demonstrated THC to be effective in pain settings have used a dose of between 3mg and 20mg, two or three times a day, with a maximum dose not exceeding 30 mg/day to avoid side effects. It is recommended to start low and use a step up phase; ‘Start low and go slow!’ In clinical trials, THC was usually given orally (by tablet, capsule or in a solution).

CBD: Clinical trials that have demonstrated CBD to be effective have used up to 150-300mg per day, and CBD was given sublingually (under the tongue) or by oral solution.

Whole plant: It is more difficult to tell the exact dose of cannabinoids in whole plant studies. Usually the THC content is detailed, ranging from 1-7% in plant material, and this is delivered as leaf, in a cannabis cigarette or vaped/inhaled. It should be remembered that when the whole plant is administered, it will contain small quantities of many other phytocannabinoids, terpenes and flavonoids that may have additive or synergistic effects (known as the entourage hypothesis) compared to isolated compounds.

Smoking CBMPs is not allowed under the new UK legislation.

Bioavailability

Phytocannabinoids have low oral bioavailability (which means that they don’t easily get into our bloodstream when taken orally) because they are highly lipophilic (fat loving) compounds. This may have played a factor in some of the negative findings in trials, therefore, alternative methods of administration may prove to be more successful in future pain trials if better delivery of CBMPs into the bloodstream can be achieved.

Some suggested mechanisms to improve phytocannabinoid drug delivery are via nano- or ionised particles, or using carriers to aid absorption in the gut. Alternatively, phytocannabinoids could be delivered via vaping, the transdermal (across the skin) route (including gels and patches), intranasal (through the nose) administration and transmucosal (across the lining of the mouth) absorption. These routes are all commonly used with existing medications for pain. Future studies are required to establish if this will enhance the effectiveness of phytocannabinoids in pain conditions.

Several studies suggest that CBMPs are better absorbed in the body when taken after food, and are therefore usually recommended to be taken with food when administered orally.

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15 https://www.fundacion-canna.es/en/flavonoids
16 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6223703/
Side-effects

In pain studies, the majority of side-effects of CBMPs were mild to moderate, but tolerable and reversible (see the below tables for more details). Typical side-effects included dizziness, dry mouth, nausea, palpitations, cough, fatigue and gastrointestinal related effects. Moderate side-effects were associated with the psychoactive effects (euphoric or dysphoric effects, mild sedation and drowsiness) and tended to be associated with higher THC doses (15-20mg). The withdrawal rates from clinical trials were higher in trials that tested THC only.

Using CBD with THC appears to reduce the side-effects of THC and mild side-effects were observed in response to Sativex and whole plant extracts. For studies that used CBD only, nausea, dry mouth, dizziness, and drowsiness were reported as common side-effects. The reported side effects of Sativex17 are dizziness, which occurs mainly during the initial titration period, nausea and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued.

Rare, but more severe, reactions to CBMPs can include psychosis, paranoia, depression, hyperemesis and diarrhoea, and are usually related to high THC levels. There is some animal model evidence to suggest, especially relating to the developing brains of children, that some of these THC-related side effects may not be reversible, and include effects on memory and behaviour.

Anecdotal evidence (see the patient testimonials) suggest that patients prefer CBMPs to traditional analgesics, which can have worse side effect profiles.

It is worth noting that traditional analgesics are fraught with side effects (some life threatening), often much less tolerable than those experienced by patients taking CBMPs. Patient testimonials suggest to us that for some people, the side effect profile of CBMPs is considerably better.

CBMP effectiveness by pain disorder

Pain represents a large area of unmet clinical need; there are many types of pain and generators of pain vary. Pain is also a variable symptom that can be daily or seasonally affected and therefore requires flexible medication. A number of common types and causes of pain that have been best explored in clinical trials using CBMPs are detailed below to identify whether particular pain conditions respond more to CBMPs.

- Multiple sclerosis (MS)-related pain

11 trials were identified examining a CBMP in MS-related pain, which are presented below in chronological order. Five have been carried out using Sativex, of which 4 studies showed significant reductions in MS-related pain and sleep disturbances. Sativex is licensed for MS–related pain in Canada. Five studies have examined THC alone, although only one of these was in large patient numbers. The smaller THC trials all showed a significant decrease in pain in MS patients, although the larger trial with dronabinol (240 patients) failed to show a significant change in pain intensity from baseline.

A summary of the clinical trials examining the effects of CBMPs in MS-related pain. Positive trials (green) saw a significant change in the primary outcome of the trial. Mixed trials (orange) failed to change the primary outcome, but showed positive effects in some of the secondary outcomes.
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- Cancer-related pain

8 trials to date have examined the use of CBMP in cancer-related pain, presented below in chronological order. 3 of these trials were carried out in larger patient numbers, all investigating Sativex. Of these, two were positive and one was negative (although the negative trial did see improvements in quality of life and sleep disruption in patients).

A summary of the clinical trials examining the effects of CBMPs in cancer-related pain. Positive trials (green) saw a significant change in the primary outcome of the trial. Mixed trials (orange) failed to change the primary outcome, but showed positive effects in some of the secondary outcomes. Red trials did not find a beneficial effect of CBMP treatment.
**Neuropathic pain**

Cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments. 15 clinical trials were identified which examined a CBMP in neuropathic pain, presented below in chronological order. In general, the outcomes of the studies tended to show a positive effect of CBMPs. Three of these trials were in larger patient numbers and all showed a positive effect of Sativex in reducing neuropathic pain. 7 studies examined the inhalation, smoking or vaporisation of whole plant extracts, and 6 of these studies were positive, but these studies were in much smaller patient numbers. Of note, CBD alone has not been tested in any neuropathic pain trials.

A summary of the clinical trials examining the effects of CBMPs in neuropathic pain. Positive trials (green) saw a significant change in the primary outcome of the trial. Mixed trials (orange) failed to change the primary outcome, but showed positive effects in some of the secondary outcomes.

A recent Cochrane review in this area\(^1\) examined clinical trial data from 1,750 participants and found that cannabis-based medicines may increase the

\(^{1}\) https://www.ncbi.nlm.nih.gov/pubmed/29513392
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number of people achieving 50% or greater pain relief compared with placebo. However it should be noted that more participants receiving cannabis-based medicines withdrew from the studies due to adverse events (including psychiatric disorders). They concluded that the potential benefits of cannabis-based medicine in neuropathic pain might be outweighed by their potential harms.
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- Fibromyalgia

Our research identified 5 trials examining a CBMP in fibromyalgia, which are presented below in chronological order. All trials showed some positive effects either in pain (with Sativex or whole plant), sleep (Sativex, THC), anxiety (Nabilone), although only Sativex has been tested in large patient numbers.

A summary of the clinical trials examining the effects of CBMPs in fibromyalgia. Positive trials (green) saw a significant change in the primary outcome of the trial. Mixed trials (orange) failed to change the primary outcome, but showed positive effects in some of the secondary outcomes.

<table>
<thead>
<tr>
<th>Title</th>
<th>Year</th>
<th>CBMP</th>
<th>Dose and treatment length</th>
<th>No. of patients</th>
<th>Results</th>
<th>Withdrawal rates</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief</td>
<td>2006</td>
<td>Delta-9-THC (local)</td>
<td>2.5-15 mg of delta-9-THC, with a weekly increase of 2.5 mg, as long as no side effects were reported. 3 months treatment.</td>
<td>9</td>
<td>Delta-9-THC had no effect on the axon reflex flare, whereas electrically induced pain was significantly attenuated after doses of 10–15 mg delta-9-THC. Daily-recorded pain of the FM patients was significantly reduced.</td>
<td>Five of nine FM patients withdrew during the study due to adverse side effects.</td>
<td></td>
</tr>
<tr>
<td>Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial.</td>
<td>2007</td>
<td>Sativex (THC:CBD)</td>
<td>Maximum of 8 sprays per 3-hour interval and a maximum of 48 sprays per 24 h. 5 weeks treatment.</td>
<td>125</td>
<td>Mean reduction in pain intensity scores was greater in patients receiving Sativex. Sativex also improved Neuropathic Pain Scale composite score, sleep, allodynia, pain disability index and Patient’s Global Impression of Change (quality of life).</td>
<td>18% on sativex and 3% on placebo withdrew during the study. 91% of Sativex group reported adverse effects compared to 77% in placebo. Most were nervous system or GI related and classed as mild.</td>
<td></td>
</tr>
<tr>
<td>Nabilone for the treatment of pain in fibromyalgia.</td>
<td>2008</td>
<td>Nabilone (THC:oral)</td>
<td>Subjects had a titrated dose; 5 mg PO at bedtime to 1 mg BID over 4 weeks.</td>
<td>40</td>
<td>There were no differences from baseline after 2 weeks of treatment. However, at the 4-week follow-up visit, nabilone significantly improved the VAS, FIQ, and FIQ anxiety scale. Depression and fatigue scales on the FIQ were not significantly different from baseline values.</td>
<td>5 from treatment and 2 from placebo dropped out.</td>
<td>Nabilone was generally well tolerated by participants throughout the study. Typical reported side effects were: drowsiness, and dry mouth.</td>
</tr>
<tr>
<td>The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial.</td>
<td>2010</td>
<td>Nabilone (THC:oral)</td>
<td>0.5-1.0 mg for 2 weeks</td>
<td>31</td>
<td>Nabilone was effective in improving sleep in patients with FM. No effects on pain, mood, or quality of life were observed.</td>
<td>29 completed</td>
<td>Mostly mild to moderate; dizziness, nausea, and dry mouth.</td>
</tr>
<tr>
<td>Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single-centre study</td>
<td>2018</td>
<td>Whole plant administration via smoking or vaporization</td>
<td>20 grams of medical cannabis therapy (1:1 THC to CBD). An option to increase the dosage to 30 grams per month was offered at 3 month 6 months treatment.</td>
<td>31</td>
<td>MCT significantly improved all patient reported outcomes and range of spine motion.</td>
<td>3 patients dropped out from the study from the initial 34 recruited</td>
<td>Mild, Red eyes in 28 of 31 patients, increased appetite in 5 of 31 patients, and sore throat in 3 out of 31 patients.</td>
</tr>
</tbody>
</table>

Potential drug-drug interactions (DDIs)

As with all medicines, the potential for drug-drug interactions (DDI) is present with CBMPs, and warnings are present in the patient information sheets for Epidiolex and Sativex regarding this. Dose adjustment of other co-administered drugs may be required because of the ability of CBMPs to interfere with the metabolism (breakdown) of medicines in the liver.

In epilepsy, DDIs have been reported between CBD (Epidiolex) and medicines that are metabolised by the liver enzymes CYP2C19 and CYP3A4, where
CBD inhibits the metabolism of anti-epileptic medicines normally broken down by these enzymes. On occasion dose reductions of other medications that have been inhibited by CBD have been necessary, this is most common with Clobazam. It is thought that some of the adverse effects observed with CBD medications may actually result from concurrent medication whose plasma concentrations are raised due to the inhibition of metabolism by CBD. There is also one case report of a DDI between CBD and warfarin, possibly because of competitive inhibition at CYP2C9 or CYP3A4.

In clinical trials with Sativex, no clinically apparent DDIs have been observed.

Cannabis-based medicines and driving

It is an offence to drive whilst impaired through drugs (whether due to non-medical use of drugs or due to legitimate use of medicines) in Section 4 of the Road Traffic Act 1988. There is also a new offence which refers to driving, attempting to drive or being in charge of a vehicle with a specified controlled drug in the body, in excess of a specified limit (Section 5A of the Road Traffic Act 1988 as amended in April 2013), which includes THC set at a very low limit.

It is a driver’s responsibility to decide whether they consider their driving is, or they believe might be, impaired on any given occasion. Based on existing best practice, current advice given to patients about issues related to ‘medicines and driving’ typically covers the following points, as relevant to each case:

1. Not to drive if any symptoms or signs develop suggesting that their driving may be impaired, such as experiencing sleepiness, poor coordination, impaired or slowed thinking, dizziness, or visual problems.

2. Not to drive at certain times when the risk may be temporarily increased, for example, when first starting, or when first increasing or reducing the dose of, a medicine that may potentially impair their driving.

3. To take particular care in circumstances that may increase the risk of their driving being impaired whilst taking their medicine, and to avoid driving if this occurs.

4. To be aware that alcohol taken in combination with other impairing drugs can substantially increase the risk of accidents.

It should be remembered that while THC is the most likely compound to cause impairments in driving, some of the side-effects of CBD are dizziness and drowsiness, so patients should take care with CBD products.

If you are stopped by the police, a new ‘medical defence’ can be raised for the offence if drivers are taking medication as directed and found to be over the limit and not impaired19.

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Cannabinoids and opioid-sparing effects

Cannabinoid and opioid receptor are expressed in several brain regions involved in the regulation of pain, and have been shown to co-localise (be expressed next to each other on the cell membrane). For this reason, scientists have researched whether cannabinoids and opioids can influence each other’s activity and ability to reduce pain. Numerous animal studies have shown that there is a synergistic effect from opioid and cannabinooid co-administration\(^20\).

To establish whether this is also true in the treatment of patients, a number of studies have investigated the effects of medical cannabis on opioid use within pain patients. A study in 2016 showed that medical cannabis use is associated with 64% lower opioid use in 244 patients with chronic pain. A more recent study from Michigan published in 2019 showed that approximately 80% of 1,321 chronic pain patients reported substituting cannabis for traditional pain medications (53% for opioids, 22% for benzodiazepines), citing fewer side effects and better symptom management as their rationale for doing so\(^21\). A 2017 study found that 37 chronic pain patients who enrolled in a Medical Cannabis Program were more likely to stop or reduce their opioid prescriptions compared to 29 non-enrolled patients\(^22\). Data from Canada published in 2019 also suggests that patients report they are using less opioids and other analgesic drugs, alcohol, tobacco, and illicit substances\(^23\).

Together, this suggests that cannabis use for chronic pain may lead to reductions in opioid usage, a theory which should be tested more rigorously through further clinical trials.

Upcoming clinical trials in the pain setting

There are 29 trials active registered on clinicaltrials.gov investigating CBMPs in pain. The majority of these trials are all located in the US, Canada and Israel, which is reflective of the fact the cannabis use for medicinal reasons has been legal in these countries for many years.

<table>
<thead>
<tr>
<th>Phase 2 trials</th>
<th>CBD</th>
<th>THC</th>
<th>THC:CBD (1:1)</th>
<th>THC:CBD other ratios</th>
<th>Whole plant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Chronic non-cancer pain</td>
<td>1 Low back pain</td>
<td>1 Chronic non-cancer pain</td>
<td>1 Pancreatic cancer (palliative)</td>
<td>2 Cancer pain</td>
</tr>
<tr>
<td></td>
<td>1 Arthritis</td>
<td></td>
<td>1 Cancer pain</td>
<td>1 Low back pain</td>
<td>1 HIV neuropathic pain</td>
</tr>
<tr>
<td>Phase 3 trials</td>
<td>1 Medical abortion pain</td>
<td>1 Chronic pain</td>
<td>1 Chronic pain</td>
<td>1 Cancer pain</td>
<td></td>
</tr>
</tbody>
</table>

\(^{20}\)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5520783/
\(^{21}\)https://www.ncbi.nlm.nih.gov/pubmed/30690169
\(^{22}\)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5690609/
\(^{23}\)https://www.ncbi.nlm.nih.gov/pubmed/30691503
Patient testimonies

Carly Jayne Barton

‘I was diagnosed with neuropathy and fibromyalgia following a stroke in my twenties. Alongside hundreds of neurological symptoms; my most dominant pain experiences were: Allodynia throughout all of my upper torso, chronic widespread and intractable neuropathic pain, involuntary movements and prolonged spasticity. These were often triggered by very benign and sometimes undetectable sensory events, such as certain types of lighting, sounds, smells, stress, hormones, temperature etc. The pain was constant and never dipped below a 7/10.

I was initially given Barbiturates, Gabapentinoids, Benzodiazepines, mild Opiates and sleeping tablets. None of these treatments helped my symptoms and so stronger doses of opiates were prescribed, this eventually lead to high doses of Morphine and Fentanyl being introduced. For every increase in dose I got some mild relief; however after a period of 8 weeks the pain levels were just as bad, if not worse than before. I felt increasingly depressed, my pain was getting worse, I was not able to function and the side effects were intolerable. These included: opioid induced hyperalgesia, feelings of worthlessness, depression, cognitive decline, seizures, absences, lack of motor control, visual disturbances, speech issues, memory loss, apathy, dizziness, drowsiness, weight loss etc.

My body also became very quickly dependent on the opiates and I would have terrible withdrawal symptoms if I forgot to change a patch or missed a few doses.

The experience of cannabis was totally different. Rather than feel that my cognitive functioning was being impaired by treatment, I found that when I would consume cannabis my memory would be better, as would my word recall and ability to process language. Where as with opiates I could bring pain down from an 9/10 to a 5/10 within quarter of an hour, inhaled cannabinoids have the ability to bring that same pain down to a 2/10 in the space of 3-4 minutes. Regular dosing means that I can mostly escape the likelihood of my pain extending over 6/10 on most days. Maintaining homeostasis for me means my Central Nervous System is less likely to be reactive. In that sense Cannabis is both a preventative and a rescue treatment for me. In terms of side effects: When I initially began consuming I would feel a change in mood quite soon after consumption, I experience a dry mouth, which means that I naturally drink more fluids throughout the day. I sometimes feel drowsy with certain strains, which can be helpful to sleep - this is easily rectified by making the right strain choices at the right time of day.’
Julie Durrans

‘Three years ago I was so unwell I had to sell my travel agency business. At that time I was taking prescribed Gabapentin, diazepam, codeine, naproxen, fluoxetine and lansoprazole. I was in severe pain, couldn’t walk far, used crutches when I did and had no energy plus severe brain fog. I began using cannabis to treat pain symptoms and found relief enough to begin physio and Pilates plus swimming. My health slowly improved. I moved 2 years ago to an area with a cannabis club and started to educate myself into everything I could to do with weed. I made oils and tinctures, edibles and learnt what strains work and what didn’t.

A year ago I began reducing my pharmaceuticals. Today I just take half the dose I was on of fluoxetine and I have codeine for emergency use but rarely take. I still have pain flare-ups but mostly I can control them quickly and keep them at bay. Exercise is easier. I’ve reduced my weight by 3 stone. The brain fog is massively reduced.

My love for cannabis as medicine has become my passion. I feel well enough to consider a return to work. I’m researching starting up a new business. A small tour operator to take patients to Jamaica to learn how cannabis might help them using legal and prescribed cannabis.’

Stephen Spencer

‘First had problems with my right shoulder (right handed) four weeks after the birth of my first child. This was later diagnosed as mild FSH Muscular Dystrophy. I was prescribed the following but all had side effects I could not live with:

Naproxen and Lansoprazole - cause abdominal cramps and stomach tenderness.
Co Codamol (highest strength) - made me zombie like and gave me terrible constipation which was very painful.
Amitriptyline - this made me have suicidal thoughts.
PreGabalin - this messed with my head, I didn’t know where I was or why I was there, complete zombie. Plus just dropping 10mg caused me to have three days of flu like symptoms from withdrawal.
Tramadol - Made me snappy and irritable when not using it, caused an anxiety attack, I would see double, I was not connecting with life at all, couldn’t remember anything.
Baclofen - after suffering the side effects of the other drugs I read about this one first and decided it was too dangerous and did not take it.

After going through all of these over the course of a year. I had a car crash when we were six weeks pregnant with our second child. I then developed Fibromyalgia which affects my right arm, both hands, my lower back, my hips, my legs and my feet. I waited 7 months for a pain clinic appointment, but when I got
The use of Cannabis-based medicinal products (CBMPs) in pain

there he did not care about my FM he was only bothered about my shoulder, offered me a steroid injection which I refused because my shoulder wasn’t the issue at the time. I asked about Sativex but no one would discuss it. That is when I decided to use cannabis. I have now used cannabis to treat ALL of my symptoms everyday for the past four and a half years. Use about 1 gram a day, I vapourise it, use RSO and make canna butter. It has saved my life, I can sleep, eat, pain is bearable, my mobility is better and most importantly I can feel like and be me. Pain can be gone or manageable in seconds to minutes, I can wipe out any bouts of fatigue in seconds, I eat, without it I have zero appetite and I sleep, on cannabis insomnia is not an issue. Which means everything else is easier to deal with. But I have to be a criminal to use it and it is very costly. My illnesses have taken my life away, I can’t work, I can barely walk, but cannabis gives me hope of some sort of a normal life without persistent torture.’

Georgina Downs

‘I have had a diagnosis of Fibromyalgia, Osteoarthritis, Osteoporosis, Ehlers Danlos Syndrome, Migraine, Morton’s Neuroma, Plantar Fasciitis, Degenerative Spine Disease, Depression and Diverticulitis, amongst others. In this time my doctors have tried to treat my pain with Amitriptyline, Nortriptyline, Gabapentin, Duloxetine, 30/500 Co-codamol, Immigran, morphine patches, voltarol patches and many, many more. Taking the above pharmaceutical medication has given me many unwanted and serious side effects and some of them have made me feel extremely ill. Not to mention the cost to the NHS. I remain in constant debilitating pain, bedridden at times and unable to enjoy even simple things like making a cup of tea or sitting in an armchair to watch TV.

Last year I have tried CBD with some degree of success. For the past 6 months, I have been able to try some pastes with combinations of THC/CBD. These have helped a great deal, they calm my pain down so that my first thought isn’t “I want a cup of tea but I can’t bear the thought of the pain it would cause, to get up and make one”. Using the THC I can get out of bed, wash my hair, get downstairs and sit in a chair! It doesn’t make me high, but it does uplift my mood. It makes me feel like continuing my hobbies like watercolour painting. It also helps me to get a good restful nights sleep, essential for Fibromyalgia sufferers, and in addition to that, I have been able to cope with the nausea caused by weaning myself off of the Duloxetine.

At the moment I am recovering from an operation to my foot and I have found that the THC has helped me cope with the post surgery pain. Relieving my pain with THC has meant that I am breaking the law for the first time in my life! I have a constant worry that I will run out and have to resort to the opiate painkillers that I have prescribed for me, and suffer the side effects of constipation, drowsiness, painful stomach aches etc.

I am unable to work, I cannot afford the cost of sourcing my THC pastes from abroad, but I don’t want to put myself at risk of trying to find “Street Weed” of which I would have no idea of what I am getting or how it will affect me. I need safe, legal access to my choice of pain relief, I want to be able to relieve my pain without causing harmful side effects. I don’t want to dread running out of my pain killing THC.’
**Mrs June Wray**

’I write about my experience of CBD...I have been down the path of prescribed medicines for pain, all of which went on to give me other medical problems mainly severe constipation severe tiredness and on one occasion a really bad experience. All of the prescribed medications do have a serious side effect on other organs of your body too.

With CBD I have not suffered further problems to my health, in fact had an amazing experience after its first use. I used the flowers of CBD after they were ‘treated’ by heat. I mixed them with chocolate. I am a non-smoker. The reason I used it was to see if it would help my ‘mesh injured body’ with pain it is in as a result of two implants. I have also suffered two strokes in 2013/4 the last one cost me my short call memory and the loss of some long term too to some extent.

After my first use of trying the chocolate I had made I had an amazing result not as much to my pain but to the effect on my memory...It was amazing how the ‘cotton wool’ feeling I had had in my head ‘lifted’ It was unbelievable to be honest. I have tried twice stopping its use only to go back to the ‘cotton wool’ effect again. My memory is in a better state too. I think it is both cruel and evil to deny a person any help with this herb. I am using 18% strength of CBD it helps my body relax too thus helping with pain but not completely freeing my body to live a better life of which I wish it could.

I do believe that it may need a higher element of THC to aid this. But that is not allowed but it should be looked into. I have discussed this with my doctor too. As a result of this I no longer take prescribed pain relief the medications I was talking were harming my body rather than help it my pain was not helped by legal medication. The only thing in my experience that has helped me has been the CBD but it needs an element of THC or if there’s a higher element of CBD. I would be willing to try it. I have suffered no side effects with CBD.’

**Anonymous**

’I suffer from chronic pain due to osteoarthritis of my hips having been prescribed various drugs over the past few years eg Dichlorfenac, Nefopam Codein all of them have very serious side effects as you should know. For the past 3 years I have been prescribed Tramadol but only use it very sparingly in the evening if pain becomes intense. I have found that by using a very small amounts of cannabis I can go weeks or months without using Tramadol at all and only taking paracetamol. Cannabis seems to facilitate joint movement rather than dulling the pain, it also has its drawbacks and I have had to experiment using myself as the guinea pig due to the lack of truthful advice available. Luckily it is not possible to overdose on cannabis and it is not highly addictive. I would love to have a reasoned discussion about how this could fit into a pain management programme but I have felt uneasy about openly giving any information about dosages delivery methods sources etc. My subjective view is that cannabis could replace opiates for many cases of chronic pain but the main obstacle at the moment is the threat of arrest and prosecution which kills any attempts to develop innovative solutions by sharing information openly.’
Lucy Stafford

‘I am a 19 year old student who uses cannabis medicinally and it has allowed me to begin to get my life back. I am diagnosed with gastro-intestinal and bladder failure and Ehlers Danlos Syndrome. This means that I cannot eat, drink or take medication orally or via feeding tube, so am dependent on intravenous nutrition through a central line at home. My condition causes severe pain as my joints dislocate regularly, as well as nausea, muscle spasm and fevers.

Before I started using cannabis, my jaw had been dislocated for a month and I was on fentanyl which didn’t even touch the severe pain. There were no options of any medications, surgeries or treatment. I had hope from my doctor that I could be prescribed Sativex when the law changed in November, however this was not the case. Out of desperation for pain relief, I tried vaporising cannabis and noticed an immediate improvement. Continuing to use the cannabis over time has allowed my jaw to come out of spasm and even back into place. Aside from my jaw, cannabis eases my other joints, bladder spasms, nausea, anxiety and has allowed me to stop almost all medications. I also have not had any sort of infection or been hospitalised since I started using cannabis 5 months ago, which has not happened in years. I have so much more energy and am able to lead my own life for the first time.

I hope that in the future patients will not be criminalised for seeking the treatment that can change their life. I hope that one day I will be able to seek professional advice on the best strains of cannabis to treat my symptoms as I am sure I would improve further. I hope that the medical community can welcome medicinal cannabis as a treatment for a wide range of chronic, debilitating illness.’

Clinician’s testimonies

Craig Blinderman

‘As a palliative care physician, I routinely witness the limits of medicine—both in terms of curing patients with an advanced illness and in terms of the pharmacological options available to treat an array of symptoms associated with a serious illness, like cancer.

Indeed, I feel like I am disappointing my patients when I tell them that we have no good treatments for anorexia. I grow frustrated when I am unable to reduce the dose of opioids for patients with chronic pain. And I feel inadequate when I am unable to successfully ameliorate refractory nausea and vomiting. In short, I feel as if I do not have sufficient pharmacological options to provide the kind of palliation that patients need.

With the passage of the Compassionate Care Act in July 2014, physicians in New York State were allowed to legally certify patients to use medical marijuana to treat an array of symptoms, giving physicians like myself another tool in the treatment of disabling symptoms, like pain. I enrolled in the
program early on as a prescriber and have certified and counselled hundreds of patients over the past few years.

I have witnessed a significant number of desperate patients find relief from their troubling or refractory symptoms, such as pain, nausea, and anorexia. I have treated chronic pain patients, sickle cell patients, cancer patients, and a number of other patients with serious illnesses, like ALS and Parkinson’s disease. Most notably, I have seen a significant dose reduction in patients receiving chronic opioid therapy for pain. This is an important outcome given the ongoing opioid crisis in the US.

While there may be significant benefits for many patients, marijuana is not a panacea. Moreover, medical marijuana is not for everyone. Elderly patients with poor metabolism or renal dysfunction, those suffering from severe psychiatric illness, or those taking multiple medications metabolized through the CYP1A2, CYP3A4 and CYP2D6 can all be at risk for serious side effects of marijuana. There are also growing concerns that medical marijuana may increase cardiovascular events, like stroke and myocardial infarction, and can increase the risk of motor vehicle accidents, as well as other side effects. Therefore, any major change in legislation to legalise marijuana for medical purposes should include a rigorous analysis of the benefits and harms to the public.

Carole Harris

‘I am the doctor mother of a 30 year old splendid young man. Josh, who suffers from autism but even more so from severe neuropathic pain. It is the latter which blights his life and renders him effectively housebound. The nerves to his bladder and bowel have been damaged and as a result he very often struggles to both urinate and defecate. The pain and frustration can overwhelm him and drive him to “meltdown”.

Over the past 10 years or more, in an attempt to alleviate his pain, we have sought the opinion of experts at home and abroad and have tried countless interventions, conventional and alternative; sane and insane. We progressed from simple analgesics up the ladder. Many of the therapeutic agents have to be introduced very slowly and a large investment of time elapses before the ideal dosage is achieved only to find that not only is it ineffective but also that its side-effects further compound the sphincter issues he already endures. Withdrawal of the drugs is, by necessity, lengthy and laborious. We have been driven to use opiates with great reluctance, fully cognisant of the risks involved.

Guidance was sought from American experts in the use of cannabinoids. Treatment with Charlotte’s Web Advance commenced in summer or 2018, using a tiny initial dose of 0.1ml. To our absolute amazement after one day, for the first time in some 5 months, he asked to go out, got dressed and was able to manage without any analgesics. This incredible benefit lasted 7 days and then unravelled. It was a wonderful window of what is possible. A validation of our conviction that he still existed as a person inside all that suffering. However, it was a bitter blow to see it all disappear. We have not been able to find that place again.
Several months ago we introduced Sativex procured at considerable expense. Under the guidance of an expert from the USA, we cautiously increased the dose. We saw no benefit but were unable to continue to the ceiling recommended because it was financially not viable.

We are stuck. We cannot try CBD products at this stage because two of the drugs he is on potentially adversely affect the ECG and to introduce a third such as CBD would be reckless. (Sativex does not have this associated risk); We were unaware of this problem when we used the Charlotte’s Web. It is a struggle to wean him off the drugs he is on because we have no effective alternative. (Even though his current regime is inadequate it is better than nothing!). Although we have tried to enlist the help of a NHS pain specialist so far have not found one prepared to do a domiciliary visit, even if we paid him privately, and understandably, a doctor cannot prescribe for a patient he hasn’t seen. Josh cannot leave the house to get to a clinic!

So, we battle on groping for a better way to get a life for Josh. It has not always been thus as the website will testify www.joshuasplanet.co.uk.

Summary

The use of CBMPs for the treatment of pain is now legal in the UK, although not recommended by the Royal College of Physicians or the Faculty of Pain Medicine of the Royal College of Anaesthetists (with the potential exception of in the palliative care setting). Despite this, there is wide-spread self-medication of pain sufferers with cannabis-based products to relieve pain and comorbidities such as sleep problems and anxiety. Several products appear to be beneficial including whole plant and extracted phytocannabinoids, although more robust evidence in large patient groups is likely to be required, especially for any future positive NICE recommendation. Anecdotal and clinical trial data suggest that the side-effects of CBD are usually mild and tolerable, although potential drug-drug interaction should be considered. Side-effects of THC alone, especially in higher concentration, may be moderate or even severe, and often leads to cessation of treatment. International use of CBMPs in pain show emerging evidence of opioid sparing effects. UK-based research in this area is limited to date, but there is growing patient appetite, clinical interest and industrial funding in the potential of CBMPs, so the future looks positive.

Acknowledgements

We would like to acknowledge the peer review, advice and suggestions that we received in the assembly and production of this report from patients and clinicians (Dr Matt Brown), scientists (Dr Stephen Alexander) the UPA, charities (XXX??), partners (Sativa investments), and the core members of the CMC.

References?