CENTRE FOR MEDICINAL CANNABIS

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

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Foreward

The Centre of Medical Cannabis (CMC) has commissioned a series of reports on the therapeutic potential of Cannabis-based medicinal products (CBMPs) in a range of disorders for which CBMPs are commonly used, of which this report is the first. The aim of this report is to be an educational tool and resource for patients and their families, carers and healthcare providers. To ensure we included the right material, we sought the input and feedback from relevant stakeholders (patients, scientists, clinicians and charities) from the beginning and throughout the process. As this is an evolving research area, we plan to revise the report regularly. We have set out the evidence for CBMPs use in pain based on the published literature of scientific research, survey data and clinical trials, covering the key issues such as doses, bioavailability, side effects and drug-drug interactions. The report concludes with testimonies from patients and doctors on their experiences with CBMPs in pain. If you would like to input on feedback on the next version of this report, please email **pain@thecmcuk.org**.

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 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. Evidence from clinical trial data suggests several products appear to be beneficial including whole plant and extracted phytocannabinoids, although more robust evidence in large patient groups is required, especially for any future positive National Institute for Health and Care Excellence (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 or THC-dominant products, especially in higher concentrations, 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 on the use of CBMPs in pain is limited to date, but there is growing patient appetite, clinical interest and industrial and government funding in the potential of CBMPs, so the future looks positive.

Glossary

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

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

CB_1: the first identified cannabinoid receptor

CB_2: 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: Δ^9-tetrahydrocannabinol, an abundant metabolite of the *Cannabis* plant that causes the 'high'

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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)[1]. 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[2].'* 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[3].'* 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[4]. 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.

[1] https://www.gov.uk/government/news/government-announces-that-medicinal-cannabis-is-legal
[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/indevelopment/gid-ng10124

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 Δ^9-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), increased appetite, 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[5], and is evidenced to be useful in a wide range of disorders such as epilepsy, schizophrenia, post-traumatic stress disorder (PTSD) and stroke[6].

The definition of a cannabinoid 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 (see below) 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 (called receptors) on the surface of our cells that recognise and bind cannabinoids, resulting in a change in the function of these proteins. This leads to the effects we recognise when people consume *Cannabis* preparations. The first receptor discovered was called the cannabinoid receptor 1 (CB_1). Activation of CB_1 is the way THC brings about most of its biological effects such as euphoria, appetite stimulation and analgesia. The CB_1 receptor is found all over the body, but has particularly high levels across the brain. The second cannabinoid receptor, called cannabinoid receptor 2 (CB_2) was discovered a couple of years later. It is expressed particularly in cells of the immune system, but levels of this receptor are increased in many tissues whenever 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 molecule derived from fatty acids called arachidonoylethanolamine (also known as anandamide, AEA). AEA is similar to THC in that it can activate both CB_1 and CB_2. A second compound called 2-arachidonoylglycerol (2-AG, also activates CB_1 and CB_2) 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.

[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5595771/
[6] https://www.sciencedirect.com/science/article/pii/S1043661816000396?via%3Dihub

The endocannabinoid system is involved in almost every biological function in the body, and particularly in the central nervous system, which is why there is a role for cannabinoids in the modulation of 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:

- 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.
- Products that have a CBD:THC ratio of 1:1 (such as Sativex[7], which is licensed internationally for spasticity in MS. However, it should also be recognised that Sativex also contains other plant products in small quantities).
- THC only products (such as nabilone[8] (a molecular similar to THC, licensed in the US and UK) and dronabinol[9] (a synthetic version of THC, licensed in the US), which are licensed for HIV/AIDS induced anorexia and chemotherapy induced nausea and vomiting).
- CBD only products (such as Epidiolex[10], which is licensed in the US for seizure reduction in epilepsy).

Evidence exists in the form of clinical trial data and patient testimonies that each 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[11]. This self-administered questionnaire investigated the extent and range of consumption of cannabis for medicinal purposes and was conducted from July to August 2018. 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 listed separately as primary reasons for medicinal cannabis use. Together, 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 UK 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.

[7] http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2033379.pdf
[8] https://bnf.nice.org.uk/drug/nabilone.html
[9] http://marinol.com/
[10] https://www.epidiolex.com/
[11] https://www.upalliance.org/2018-upa-patient-survey-results

Surveys from other countries

A survey carried out in north-eastern US and published in 2017 found that 64% (of 1,513 patients) were using *Cannabis* for chronic pain. In Canada, a survey of 628 consumers of *Cannabis* for therapeutic purposes in 2013 showed that 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 across the globe.

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% versus 20%). 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[12] 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[13], the top three medical conditions reported were chronic pain, arthritis/joint pain, and anxiety. Almost 36% of respondents reported that CBD treated their medical condition "very well by itself".

Together, this suggests there is no major preference amongst patients for either THC-dominant or CBD-dominant products in the treatment of pain. 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[14].

THC

Δ^9-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 of THC in pain mainly involves activation of the

[12] https://daks2k3a4ib2z.cloudfront.net/595e80a3d32ef41bfa200178/59946dd86c6b200001c5b9cb_CBD_-_HelloMD_Brightfield_Study_-_Expert_Report_-_FINAL.pdf
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6043845/
[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5554313/

CB_1 receptor, causing inhibition of the transmission of pain signals. The pain-relieving effects of THC can also involve CB_2 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 to enhance the function of glycine receptors which modulate nociception (the perception of pain) in animal studies.

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 CB_1 or CB_2 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 clinical evidence base for the use of CBMPs in patients with pain was considered, a total of 69 clinical trials published between 1975 and 2018 were identified. A full reference list of all the clinical trials included in this analysis can be found at the end of the report by CBMP type.

The majority of these studies were small in size, and only 11 of these trials involved more than 100 patients. 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 of CBMPs in reducing pain. It is on the basis of multiple small studies that the evidence base for CBMPs in pain is largely held to be inadequate. It is also very difficult to judge how effective CBMPs are in pain based on this clinical trial data because of the different types of CBMPs tested, by different routes of administration, carried out in very different patient populations across trials. 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

BBecause 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 (77% of trials positive for their primary endpoint) or Sativex (65% of trials

positive for their primary endpoint) were more likely to show an improvement in pain ratings (both patient and clinician reported) across a range of pain settings compared to THC alone (46% of trials positive for their primary endpoint). Patient testimony to this effect can be found here[15]. Only three, small clinical trials examining the effects of CBD in pain have been published to date, but all were positive.

	Whole plant	Sativex	THC	CBD
Total number of studies	**14**	**17**	**36**	**3**
Positive trials	11 (79%)	11 (65%)	16 (44%)	3 (100%)
Negative trials	2	1	12	0
Mixed results	1	4	7	0
Positive trials with >100 patients	**1/1 (100%)**	**6/8 (75%)**	**1/2 (50%)**	**0**
Pain conditions improved in positive trials	Chronic pain, neuropathic pain, fibromyalgia, spinal cord injury, diabetic neuropathy, pain associated with Multiple sclerosis, HIV-associated neuropathy	Pain associated with Multiple sclerosis, cancer-related pain, neuropathic pain, diabetic neuropathy, pain due to rheumatoid arthritis	Multiple sclerosis, chest pain, diabetic neuropathy, headache, neuropathic pain, spasticity-related pain, chronic pain, cancer-related pain	Post-operative pain, dysautonomic syndrome, neuropathic pain
Route of administration	Tea, smoked, vapourised, inhaled	Sublingual spray	Oral (tablets, capsules, solution, sublingual spray)	Sublingual spray or oil

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/endpoint (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

[15] https://www.upalliance.org/blog/2017/8/3/cannabis-and-sativex-

impression of change and quality of life. This data is in agreement with the anecdotal evidence and testimonies from CBMP-using pain patients who feel that CBMPs holistically improves 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 (under the tongue).

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 between 150-300mg per day, and CBD was given sublingually or by oral solution.

Whole plant: It is more difficult to tell the exact dose of cannabinoids administered 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[16] 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 if insufficient quantities of relevant compounds enter the bloodstream. Alternative methods of administration (which many researchers and companies are trying to achieve) may prove to be more successful in future pain trials if better delivery of cannabinoids into the bloodstream can be achieved. Some suggested mechanisms to improve cannabinoid drug delivery are via nano- or ionised particles, or using carriers to aid absorption in the gut. Alternatively, cannabinoids 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[17].

[16] https://www.fundacion-canna.es/en/flavonoids
[17] 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 i.e. stop when the medication is stopped (see the below tables for more details). Typical side-effects include dizziness, dry mouth, nausea, palpitations, cough, fatigue and gastrointestinal related effects. Moderate side-effects were associated with the psychoactive effects of CBMPs (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 medicines.

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 Sativex[18] 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.

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, and there are many types and generators of pain. 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 better 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 four 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.

[18] http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2033379.pdf

Title	Year	CBMP	Dose and treatment length	No. of patients	Results	Withdrawal rates	Side effects
Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial.	2004	Dronabinol (THC)	2.5 mg daily, and increased by 2.5 mg every other day to a maximum dose of 5 mg (two capsules) twice daily. 3 weeks treatment.	24	Median spontaneous pain intensity was significantly lower during dronabinol treatment. On the SF-36 quality of life scale, the two items bodily pain and mental health indicated benefits from dronabinol.		Adverse events, including dizziness, were more frequent with dronabinol than with placebo during the first week of treatment.
Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis.	2005	Sativex (THC:CBD)	Up to 48 sprays (THC 129.6 mg:CBD 120 mg) in 24 hours. No more than 8 sprays in 3hrs and no more than 50% of previous days dose. 4 weeks treatment.	64	Sativex was effective in reducing pain and sleep disturbance in MS related neuropathic pain. No difference in anxiety or depression using Guy's Neurological Disability Scale	97% completion rate	Well tolerated, although more patients on Sativex reported dizziness, dry mouth, and somnolence. Cognitive side effects were limited to long-term memory storage.
Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis--secondary publication	2005	Dronabinol (THC)		24	Dronabinol reduced the spontaneous pain intensity significantly compared with placebo		ARTICLE NOT IN ENGLISH
Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial.	2007	Sativex (THC:CBD)	< 8 sprays within any 3 hours and up to 48 sprays in 24 hours, with a maximum increase of 50% in the number of sprays tolerated in the previous 24 hour period. Mean treatment length 463 days, SD 378 days.	64	THC/CBD was effective, with no evidence of tolerance.	2 patients withdrew	Ninety-two percent of patients experienced an AE deemed to be of mild to moderate severity by the investigators. The most common of which were dizziness and nausea.
Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial.	2012	cannabis cigarette	900 mg (4% delta-9-THC by weight). 3 days treatment.	37	Smoked cannabis resulted in a reduction in patient scores on the modified Ashworth scale (change in spasticity) by an average of 2.74 points. Scores on the Paced Auditory Serial Addition Test decreased by 8.67 points more with treatment than with placebo	30 completed out of 37	No serious adverse effects
A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis.	2013	Sativex (THC:CBD)	Patients self-titrated with a max of 12 sprays in 24hrs. Phase A: 14-week treatment phase. Phase B: 14 weeks	Phase A: 339 Phase B: 42	Phase A of this study failed to show a difference between THC/CBD spray and placebo. Phase B of the study demonstrated efficacy of THC/CBD spray in improving pain. Brief Pain Inventory — Short Form, Subject Global Impression of Change, and sleep quality assessment.	Phase A: (THC/CBD spray) 141 completed, placebo 172 completed. Withdrawal 1 in phase.	THC/CBD spray 75% had at least one adverse event placebo 62%
Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.	2015	Nabilone (THC)	0.5 mg/ week increase for 4 weeks. Followed by 1mg twice daily for 5 weeks	15	Nabilone as an adjunctive to GBP is an effective, well-tolerated combination for MS-induced neuropathic pain.		Nabilone was well tolerated, with dizziness/drowsiness most frequently reported.
Dronabinol is a Safe Long-Term Treatment Option for Neuropathic Pain Patients.	2017	Dronabinol (THC)	Mean daily dose of 12.7 ± 2.9 mg for 16 weeks followed by a 32-weeks open-label period. A subgroup of patients participated in the open-label long-term safety follow-up for up to an additional 96 weeks	240 MS patients	The primary endpoint "mean change of pain intensity from baseline to mean of weeks 1–16" compared between dronabinol and placebo was not statistically significant. The observed pain reduction was clinically relevant in both groups. During long-term follow-up, pain intensities remained at a low level (range 2.5–3.3).		The proportion of patients experiencing AEs was higher in the dronabinol group. SARs were very rare and occurred only in 3 patients (dysphoria, constipation, exacerbation of pre-existing neuropathic pain). No signs of drug abuse and one possible case of dependency occurred.
Pain Modulation after Oromucosal Cannabinoid Spray (SATIVEX®) in Patients with Multiple Sclerosis: A Study with Quantitative Sensory Testing and Laser-Evoked Potentials.	2018	Sativex (THC:CBD)	7 puffs a day ("19mg THC and 18mg CBD). 1 month	19	Patients reported a significant reduction in pain. There was a significant increase in cold pain threshold by hand stimulation and a significant reduction in abnormal cold perception thresholds.	9 dropped out of the study because of drug abuse (n=1), relapse (n=1), lack of compliance with neurophysiological studies (n=4), and intolerable adverse events (dizziness) (n=3)	
Sativex® as add-on therapy vs. further optimized first-line ANTIspastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial.	2018	Sativex (THC:CBD)	Phase A: titrated the dosage of THC:CBD spray to a maximum of 12 sprays/day. 4 weeks. Phase B: Patients re-titrated dose (12 weeks)	Phase A: n=191, Phase B: n=106	Sativex led to a significant improvement in mean pain NRS (p = 0.0013) at 12 weeks vs baseline.		Adverse effects were mild/moderate. No safety concerns. All AEs were of either mild or moderate intensity except for one severe SAE reported in the placebo group.
Effects on Spasticity and Neuropathic Pain of an Oral Formulation of Δ9-tetrahydrocannabinolin Patients With Progressive Multiple Sclerosis.	2018	THC (tablet, ECP002A, Echo Pharmaceuticals)	3, 5, and 8 mg, leading to a total daily dose of 16 mg, for 4 weeks.	24	Pain was significantly reduced when measured directly after administration of ECP002A in the clinic but not when measured in a daily diary.		

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.

– Cancer-related pain

Eight trials to date have examined the use of CBMP in cancer-related pain, presented below in chronological order. Three 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).

Title	Year	CBMP	Dose and treatment length	Number of patients	Results	Withdrawal rates	Side effects
The analgesic properties of delta-9-tetrahydrocannabinol and codeine.	1975	THC	10 or 20 mg THC, 7 hours treatment	36 with pain associated with cancer	Both 10mg THC and 20mg THC reduced pain compared to placebo. 10mg THC was well tolerated and somewhat sedating, analgesic properties of THC developed gradually, were prolonged and seemed to be mild. Peak analgesic effect of 20mg THC developed at 5hr after administration.	2 did not complete	5 patients experienced adverse reactions, on on 10mg THC and 4 on 20 mg THC. More adverse effects were associated with high THC dose; including edation, mental clouding, ataxia, disorientation.
Analgesic effect of delta-9-tetrahydrocannabinol.	1975	THC	5/10/15/20mg, 6hrs	10 with pain associated with cancer	Significant trend for pain relief with increased dose. Analgesic effect of THC developed gradually and was prolonged. Blood pressue and heart rate decreased following 15 and 20mg THC doses.		Side effects were experienced by 10 patients. 20mg THC caused heavy sedation, 15mg considerable drowsiness.
Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain.	2010	Sativex	Max dose= 8 sprays in any 3hr period and 48 in a 24hr period. Two weeks treatment.	177	THC:CBD extract group showed a significant reduction in pain severity, with a reduction in mean pain NRS scores from baseline. No differences in patient-assessed sleep quality or nausea NRS scores or investigator-assessed pain control assessment. Significant reduction in cognitive function with the THC:CBD and THC groups vs placebo group.		Active compounds were generally well tolerated, and no safety concerns were identified during this study. Adverse effects were in 60% of patients most apparent: somnolence, dizziness, and nausea, mostly of mild or moderate severity.
Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial.	2012	Sativex	Either 1-4 sprays, 6-10 sprays, 11-16 sprays. Maximum duration was 9 weeks.	360	The low-dose group achieved a 26% improvement in pain compared with baseline. The study did not find an analgesic effect from the high-dose group and also demonstrated that this dose was not well tolerated. Patients receiving the low and medium doses of nabiximols recorded improvement in sleep.	263 completed; only 59 patients completed the high dose study out of 90 patients.	High dose (11-16 sprays) was not well tolerated. Adverse effects leading to withdrawal in the low- and medium-dose groups was comparable to placebo. Most common side effecrs were nausea and dizziness at higher dose.
An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics.	2013	Sativex	Patients self-administered the medication to their optimal dose with a restriction of eight actuations in a three-hour period up to a maximum of 48 sprays per 24-hour period. Mean treatment length was 25 days (range 2-579 days).	43	"pain severity" and "worst pain" domains (from Brief Pain Inventory-Short Form scores) showed a decrease at each visit in the THC/CBD spray patient a. Quality of life scores showed an improvement in insomnia, pain, and fatigue.	23 patients (59%) receiving THC/CBD spray and one patient (25%) taking THC spray withdrew because of Aes.	No new safety concerns associated with the extended use of THC/CBD spray arose from this study.
A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain.	2014	Sativex	one spray day 1, increased by one to two sprays per day until a dose was reached that helped their pain but not exceed 12 sprays per day. 4 weeks treatment.	18	There was no difference between the treatment and the placebo groups. Five participants reported a significant reduction in pain. Analysis of SF-36 (health related quality of life) and QST (sensory testing) demonstrated no effect as compared with placebo.	16 participants completed.	No serious adverse events: most common side effects reported were fatigue, dizziness, dry mouth, and nausea
Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial.	2016	Nabilone	0.5mg; same dose for an entire week, increased to two pills a day on second week; from thrid week max of 4 pills per day adjusted by radio-oncologist. 7 weeks treatment.	56	There was no difference in pain between treated (Nabilone) and placebo. Nabilone did not lengthen the time required for a 20% increase of pain. No significant differences were found during the overall treatment period in sleep and no difference in nausea in the nabilone group.	9 patients receiving nabilone quit versus 15 receiving the placebo.	There was no difference in the occurrence of any of the adverse effects of nabilone, including drowsiness, anxiety, and xerostomia. Patients receiving nabilone reported 20 other symptoms compared to 24 for controls, mostly related to radiotherapy treatments.
Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain.	2018	Sativex (THC:CBD)	27mg THC and 25 mg CBD. Max dose: 10 sprays per day. 14 day titration period, followed by 3 weeks at the titrated dose.	397: (n=199) or placebo (n=198)	Sativex not superior to placebo regarding chronic pain. Nabiximols (Sativex) was statistically superior to placebo on two of three quality-of-life instruments at week 3 and on all three at Week 5. Nabiximol showed significant improvement in sleep disruption.	8 nabiximols patients (29.1%) and 48 placebo patients (24.2%) withdrew from the study.	72.4% adverse effects reported with nabiximols vs 65.7% with placebo. Main side effects: nausea, dizziness, vomiting and decreased appetite. Overall side effects were mild. Severe side effects were <5%.

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 (12/15), the outcome of these 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. Seven studies examined the inhalation, smoking or vaporisation of whole plant extracts, and six of these studies were positive, but these studies were in much smaller patient numbers. CBD alone has not been tested in any neuropathic pain trials.

Title	Year	CBMP	Dose and treatment length	Condition	No. of patients	Results	Withdrawal rates	Side effects
A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms.	2003	Sativex (THC:CBD)	2.5 mg THC and/or CBD maximum permitted dose of each 120 mg / 24 hours. Two week treatment.	Mixed	24	Pain relief associated with both Stivex was significantly superior to placebo. Impaired bladder control, muscle spasms and spasticity were all improved by Sativex in some patients with these symptoms.	3 withdrew	Unwanted effects are predictable and generally well tolerated.
Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial.	2004	Sativex (THC:CBD)	4-8 sprays, no more than 50% of the number taken in the previous 24hrs. Max dose 8 sprays within a 3-h period and 48 sprays within any 24 h period. Baseline period of 2 weeks, followed by three, 2-week treatment periods	Neuropathic pain from brachial plexus avulsion	48	Mean pain severity score failed to fall by two points (defined by the studies hypothesis), however there was a statistically significant improvement. Sleep quality was also improved.	3 withdrew before completion	No serious adverse effects occurring throughout the study. Majority mild or moderate and resolved spontaneously.
Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial.	2007		3.56% THC or 0% THC (placebo). Dose three times daily for 5 days.	Painful HIV-associated sensory neuropathy.	50	Smoked cannabis reduced daily pain by 34%. >30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group. First cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo. Reduction in induced hyperalgesia but no effect on noxious heat stimulation.	30 patients completed the pain model	No serious adverse effects.
Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial.	2007	Sativex (THC:CBD)	A maximum of 8 sprays were administered over 2 hrs. Patients titrated their dose maximum of 8 sprays per 3-hour interval and a maximum of 48 sprays per 24 h. 5 weeks treatment.	Unilateral peripheral neuropathic pain and allodynia	125	Mean reduction in pain intensity scores was greater in patients receiving sativex than placebo. Sativex also improved Neuropathic Pain Scale composite score, sleep, allodynoa, pain disability index and Patient's Global Impression of Change (quality of life).	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.
A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain.	2008	Cannabis cigarettes	High-dose (7%), low-dose (3.5%), or placebo cannabis. 3-4 weeks treatment.	Neuropathic pain	38	No effect on evoked pain was seen.		Psychoactive effects were minimal and well-tolerated, with some acute cognitive effects, particularly with memory, at higher doses.
Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial.	2009	Cannabis cigarettes	1 and 8% THC. Four times daily for 5 consecutive days during each of 2 treatment weeks, separated by a 2-week washout.	HIV-associated distal sensory predominant polyneuropathy	34	Among the completers, pain relief was greater with cannabis than placebo. Mood and daily functioning both improved to a similar extent.	28 completed	Two subjects experienced treatment-limiting toxicities. Smoked cannabis generally well tolerated
Smoked cannabis for chronic neuropathic pain: a randomized controlled trial.	2010		0%, 2.5%, 6% and 9.4% THC. 14-day periods in a crossover trial: three times daily dose for the first five days in each cycle, followed by a nine-day washout period.	Chronic neuropathic pain: (post-traumatic or post surgical)	23	Average daily pain intensity was lower on 9.4% v. 0% tetrahydrocannabinol. Participants receiving 9.4% tetrahydrocannabinol reported improved ability to fall asleep and improved quality of sleep. no differences in mood or quality of life.	21 completed	Most common side effects at a 9.4% dose of THC: headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness and cough.
Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor.	2010	Sativex (THC:CBD)	Sativex. 2 week titration phase followed by a 10-week maintenance phase.	Painful diabetic neuropathy:	80	Efficacy of Sativex was not greater than control. EuroQOL and SF-36 (quality of life assessment) questionnaires showed improvement in both groups but not statistically significant.	6 withdrew from adverse effects. One was excluded.	
An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain.	2012	Nabilone (THC)	1–4mg/day. During the double-blind phase, subjects were assigned to continue nabilone at the effective dose achieved in the flexible-dose single-blind phase. For subjects receiving nabilone during the double-blind phase, the dose achieved at day 28 was continued without change for 5 weeks.	Diabetic peripheral neuropathic pain.	Single blind phase: 87. Double blind phase: 26	Improvement in the change in mean end-point neuropathic pain with nabilone vs placebo.	Medication-related confusion led to discontinuation in 2/37 subjects.	
Low-dose vaporized cannabis significantly improves neuropathic pain.	2013	Vaporized cannabis	Medium dose (3.53%), low dose (1.29%), or placebo cannabis.	Experiencing neuropathic pain despite traditional treatment	39	VAS pain intensity: cannabis has analgesic efficacy with the low dose being as effective a pain reliever as the medium dose.		Psychoactive effects were minimal and well tolerated, and neuropsychological effects were of limited duration and readily reversible within 1 to 2 hours.
The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study.	2014	Cannabis flower	15.1±0.1mg cannabis flos containing 3.08±0.02 mg THC for 3 seconds. Median monthly dose 20–30 g. Smoking two to three times a day.	Sufferers of neuropathic pain of any type.	10	A significant 45% reduction in pain intensity was noted 20 minutes post inhalation.	None, 2 patients were excluded based on failed devices.	Tolerable light headaches lasting 15–30 minutes requiring no intervention.
A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment.	2014	Sativex (THC:CBD)	8 sprays in a 3-h period, maximum of 24 sprays per 24-h period. Patients self-titrated medication but limited to 50% of previous day's dose. 15 week (1-week baseline and 14-week treatment period)	Peripheral neuropathic pain (PNP) associated with mechanical allodynia	303 (138 Sativex; 118 placebo)	A greater than 30% improvement in pain intensity, was reported by 28% of patients receiving THC/CBD spray compared with 16% of patients taking placebo. Secondary measures of sleep quality and subject Global Impression of Change were both significantly in favour of THC/CBD spray treatment.		Most common were dizziness, nausea, fatigue and dysgeusia (distortion of sense of taste). No evidence of tolerance developing and few patients reported experiencing severe AEs.
Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy	2015	Inhaled Cannabis	Placebo, low (1% THC), medium (4% THC), or high (7% THC) dose cannabis. % THC by weight, CBD <1%. Weight of 400 mg of plant material i.e. 0, 4, 16, 28mg THC. Four sessions, seperated by two weeks.	Painful diabetic peripheral neuropathy	16	Significant dose-dependent effect of cannabis on spontaneous and evoked pain. Average pain intensity score was 0.44 points higher than the pain score from the low dose, 0.42 points higher than the medium dose, and 1.2 points higher than the high dose.	One patient only completed two treatments.	Significant impaired performance of the high doses on 2/3 neuropsychological tests. Patients reporting euphoria (100% for high dose, 60% for placebo) or somnolence as adverse effects.
A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain.	2015	Sativex (THC:CBD)	2.7 mg of THC and 2.5 mg; max 8 sprays per 3hr period and 24 actuations every 24hr. Patients self-titrated to reach their optimum dose. 38 weeks treatment.	Peripheral neuropathic pain (PNP) associated with diabetes or allodynia.	380	Decrease in pain sccore over time. At least half of patients had a 30% improvement in pain at all time points. Sustained improvements from baseline were also observed in NPS and sleep quality scores. Also no evidence of atolerance developing towards THC/CBD spray.	234 patients completed the study (62%)	Most common treatment-related adverse effects were dizziness and nausea.
An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease.	2016	Vaporized Cannabis	4 puffs of placebo, 2.9% or 6.7% THC on 3 separate occations. Three 8 hour experiments each with a minimum of 3 days apart.	Individuals with injury or disease of the spinal cord.	42	After controlling for baseline pain, there was a significant dose effect of cannabis on pain intensity.	None	Psychoactive and subjective effects were dose dependent.

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[19] examined clinical trial data from 1,750 participants and found

[19] https://www.ncbi.nlm.nih.gov/pubmed/29513392

that cannabis-based medicines may increase the 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.

– Fibromyalgia

Our research identified five 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.

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

A summary of the clinical trials examining the effects of CBMPs in fibromyalgia.

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 impaired[20].

[20] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/325275/healthcare-profs-drug-driving.pdf

Cannabinoids and opioid-sparing effects

Cannabinoid and opioid receptors 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 now shown that there is a synergistic effect from opioid and cannabinoid co-administration[21].

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[22]. 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[23]. 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[24].

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.

	CBD	THC	THC:CBD (1:1)	THC:CBD other ratios	Whole plant
Phase 2 trials	1 Chronic non-cancer pain 1 Arthritis	1 Low back pain	1 Chronic non-cancer pain	1 Pancreatic cancer (palliative) 1 Cancer pain	2 Cancer pain 1 osteoarthritis 1 Low back pain 1 HIV neuropathic pain
Phase 3 trials		1 Medical abortion pain	1 Chronic pain	1 Chronic pain	1 Cancer pain

[21] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5520783/
[22] https://www.ncbi.nlm.nih.gov/pubmed/30690169
[23] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5690609/
[24] 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 led to high doses of Morphine and Fentynal being introduced. For every increase in dose I got some mild relief, however after a period of eight 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. Whereas with opiates I could bring pain down from an 9/10 to a 5/10 within a 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 two 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 three 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 (FM) which affects my right arm, both hands, my lower back, my hips, my legs and my feet. I waited seven months for a pain clinic appointment, but when I got 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 every day for the past four and a half years. Use about one gram a day, I vaporise 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 six 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 night's 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 postsurgery 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, Codeine all of them have very serious side effects as you should know. For the past three 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 program 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 five 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 illnesses.'

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 of 2018, using a tiny initial dose of 0.1ml. To our absolute amazement after one day, for the first time in some five months, he asked to go out, got dressed and was able to manage without any analgesics. This incredible benefit lasted seven 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.'

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, CMC partners and council of clinicians, and the core members of the CMC.

References

Clinical trials examining the effects of whole plant products on pain

1. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. (2007). Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 68: 515-521.

2. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, et al. (2012). Smoked cannabis for spasticity in Multiple Sclerosis: a randomized, placebo-controlled trial. Canadian Medical Association Journal 184: 1143-1150.

3. Eisenberg E, Ogintz M, & Almog S (2014). The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. Journal of Pain & Palliative care Pharmacotherapy 28: 216-225.

4. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gnzales J, Gouaux B, et al. (2009). Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 34: 672-680.

5. Kraft B, Frickey NA, Kaufmann RM, Reif M, Frey R, Gustorff B, et al. (2008). Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology 109: 101-110.

6. Poli P, Crestani F, Salvadori C, Valenti I, & Sannino C (2018). Medical Cannabis in Patients with Chronic Pain: Effect on Pain Relief, Pain Disability, and Psychological aspects. A Prospective Non randomized Single Arm Clinical Trial. La Clinica terapeutica 169: e102-e107.

7. Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, et al. (2007). Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology 107: 785-796.

8. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, & Atkinson JH (2015). Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. Journal of Pain 16: 616-627.

9. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal 182: E694-701.

10. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, & Donaghe H (2013). Low-dose vaporized cannabis significantly improves neuropathic pain. Journal of Pain 14: 136-148.

11. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. Journal of Pain 9: 506-521.

12. Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, & Phan A (2016). An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain from Spinal Cord Injury and Disease. Journal of Pain 17: 982-1000.

13. Yassin M, Oron A, & Robinson D (2019). Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study. Clinical and Experimental Rheumatology 37 Suppl 116: 13-20.

Clinical trials examining the effects of Sativex on pain

1. Berman JS, Symonds C, & Birch R (2004). Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 112: 299-306.

2. Blake DR, Robson P, Ho M, Jubb RW, & McCabe CS (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford, England) 45: 50-52.

3. Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lej□ko J, et al. (2015). A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. Journal of Neurology 262: 27-40.

4. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, & Fallon MT (2010). Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain. Journal of Pain and Symptom Management 39: 167-179.

5. Johnson JR, Lossignol D, Burnell-Nugent M, & Fallon MT (2013). An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manage 46: 207-218.

6. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, et al. (2013). A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of Neurology 260: 984-997.

7. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, et al. (2018). Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. Journal of Pain and Symptom Management 55: 179-188.e171.

8. Lynch ME, Cesar-Rittenberg P, & Hohmann AG (2014). A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage 47: 166-173.

9. Markovà J, Essner U, Akmaz B, Marinelli M, Trompke C, Lentschat A, et al. (2019). Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. International Journal of Neuroscience 129: 119-128.

10. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, & Haines D (2007). Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 133: 210-220.

11. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. (2012). Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial. The Journal of Pain 13: 438-449.

12. Rog DJ, Nurmikko TJ, Friede T, & Young CA (2005). Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 65: 812-819.

13. Rog DJ, Nurmikko TJ, & Young CA (2007). Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clinical therapeutics 29: 2068-2079.

14. Selvarajah D, Gandhi R, Emery CJ, & Tesfaye S (2010). Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care 33: 128-130.

15. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. (2014). A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. European Journal of Pain (London, England) 18: 999-1012.

16. Turri M, Teatini F, Donato F, Zanette G, Tugnoli V, Deotto L, et al. (2018). Pain Modulation after Oromucosal Cannabinoid Spray (SATIVEX(®)) in Patients with Multiple Sclerosis: A Study with Quantitative Sensory Testing and Laser-Evoked Potentials. Medicines (Basel, Switzerland) 5.

17. Wade DT, Robson P, House H, Makela P, & Aram J (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical rehabilitation 17: 21-29.

Clinical trials examining the effects of THC on pain

1. Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, & Bouhassira D (2004). Are oral cannabinoids safe and effective in refractory neuropathic pain? European journal of pain (London, England) 8: 173-177.

2. Beaulieu P (2006). Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Canadian Journal of Anaesthesia 53: 769-775.

3. Berman JS, Symonds C, & Birch R (2004). Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 112: 299-306.

4. Bestard JA, & Toth CC (2011). An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Practice: The Official Journal of World Institute of Pain 11: 353-368.

5. Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, & Rowbotham DJ (2003). Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. Pain 106: 169-172.

6. Cooper ZD, Comer SD, & Haney M (2013). Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers. Neuropsychopharmacology 38: 1984-1992.

7. Cote M, Trudel M, Wang C, & Fortin A (2016). Improving Quality of Life with Nabilone during Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. The Annals of Otology, Rhinology, and Laryngology 125: 317-324.

8. de Vries M, Van Rijckevorsel DC, Vissers KC, Wilder-Smith OH, & Van Goor H (2016). Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability. British Journal of Clinical Pharmacology 81: 525-537.

9. de Vries M, van Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, & van Goor H (2017). Tetrahydrocannabinol Does Not Reduce Pain in Patients with Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. Clinical gastroenterology and Hepatology 15: 1079-1086.e1074.

10. Frank B, Serpell MG, Hughes J, Matthews JN, & Kapur D (2008). Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 336: 199-201.

11. Haroutiunian S, Rosen G, Shouval R, & Davidson E (2008). Open-label, add-on study of tetrahydrocannabinol for chronic nonmalignant pain. Journal of Pain & Palliative Care Pharmacotherapy 22: 213-217.

12. Issa MA, Narang S, Jamison RN, Michna E, Edwards RR, Penetar DM, et al. (2014). The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clinical Journal of Pain 30: 472-478.

13. Kalliomaki J, Philipp A, Baxendale J, Annas P, Karlsten R, & Segerdahl M (2012). Lack of effect of central nervous system-active doses of nabilone on capsaicin-induced pain and hyperalgesia. Clinical and Experimental Pharmacology & Physiology 39: 336-342.

14. Malik Z, Bayman L, Valestin J, Rizvi-Toner A, Hashmi S, & Schey R (2017). Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial. Diseases of the Esophagus 30: 1-8.

15. Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, & Brenneisen R (2003). The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain 105: 79-88.

16. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, et al. (2008). Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. Journal of Pain 9: 254-264.

17. Noyes R, Jr., Brunk SF, Avery DA, & Canter AC (1975). The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clinical Pharmacology and Therapeutics 18: 84-89.

18. Noyes R, Jr., Brunk SF, Baram DA, & Canter A (1975). Analgesic effect of delta-9-tetrahydrocannabinol. Journal of Clinical Pharmacology 15: 139-143.

19. Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, et al. (2012). Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. Journal of Headache and Pain 13: 677-684.

20. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, & Polz W (2006). Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial. Wiener Klinische Wochenschrift 118: 327-335.

21. Redmond WJ, Goffaux P, Potvin S, & Marchand S (2008). Analgesic and antihyperalgesic effects of nabilone on experimental heat pain. Current Medical Research and Opinion 24: 1017-1024.

22. Rintala DH, Fiess RN, Tan G, Holmes SA, & Bruel BM (2010). Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. American Journal of Physical Medicine & Rehabilitation 89: 840-848.

23. Roberts JD, Gennings C, & Shih M (2006). Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. European Journal of Pharmacology 530: 54-58.

24. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, & Abramov-Sommariva D (2017). Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. European Neurology 78: 320-329.

25. Schley M, Legler A, Skopp G, Schmelz M, Konrad C, & Rukwied R (2006). Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Current Medical Research and Opinion 22: 1269-1276.

26. Seeling W, Kneer L, Buchele B, Gschwend JE, Maier L, Nett C, et al. (2006). Delta(9)-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain. Der Anaesthesist 55: 391-400.

27. Skrabek RQ, Galimova L, Ethans K, & Perry D (2008). Nabilone for the treatment of pain in fibromyalgia. Journal of Pain 9: 164-173.

28. Svendsen KB, Jensen TS, & Bach FW (2004). Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 329: 253.

29. Svendsen KB, Jensen TS, & Bach FW (2005). Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis-secondary publication. Ugeskrift for Laeger 167: 2772-2774.

30. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. (2012). An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain 153: 2073-2082.

31. Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, et al. (2015). Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Medicine 16: 149-159.

32. van Amerongen G, Kanhai K, Baakman AC, Heuberger J, Klaassen E, Beumer TL, et al. (2018). Effects on Spasticity and Neuropathic Pain of an Oral Formulation of Delta9-tetrahydrocannabinol in Patients WithProgressive Multiple Sclerosis. Clinical Therapeutics 40: 1467-1482.

33. Wade DT, Robson P, House H, Makela P, & Aram J (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical Rehabilitation 17: 21-29.

34. Ware MA, Fitzcharles MA, Joseph L, & Shir Y (2010). The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia and Analgesia 110: 604-610.

35. Wissel J, Haydn T, Muller J, Brenneis C, Berger T, Poewe W, et al. (2006). Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. J Neurol 253: 1337-1341.

Clinical trials examining the effects of CBD on pain

1. Cunetti L, Manzo L, Peyraube R, Arnaiz J, Curi L, & Orihuela S (2018). Chronic Pain Treatment With Cannabidiol in Kidney Transplant Patients in Uruguay. Transplantation proceedings 50: 461-464.

2. Palmieri B, Laurino C, & Vadala M (2017). Short-Term Efficacy of CBD-Enriched Hemp Oil in Girls with Dysautonomic Syndrome after Human Papillomavirus Vaccination. The Israel Medical Association Journal : IMAJ 19: 79-84.

3. Wade DT, Robson P, House H, Makela P, & Aram J (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical rehabilitation 17: 21-29.