

Should doctors prescribe cannabinoids?

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The medical use of cannabis was advocated in the United States in the 1970s and 1980s when clinical trials of oral synthetic tetrahydrocannabinol (THC) and other oral synthetic cannabinoids reported efficacy in controlling nausea in patients with cancer who were undergoing chemotherapy. Dronabinol (an oral synthetic THC) was approved by the Food and Drug Administration in 1985 for this indication, but it was not widely used because patients were unable to titrate doses or disliked its psychoactive effects. It is still available in the US, United Kingdom, and the rest of Europe.

Box 1 outlines the different formulations of cannabinoids, the term we use for the sake of clarity and convenience to refer to synthetic cannabinoids and drugs derived from the cannabis plant, such as nabiximols. Box 2 lists indications for which cannabinoids have been approved for medical use.

Box 1: Forms of cannabis and cannabinoids

Cannabis: Any product of the *Cannabis sativa* plant (such as marijuana or hash) that is smoked for its psychoactive effects

Cannabinoids: This term usually refers to a group of different chemical compounds that activate cannabinoid receptors in the body, including marijuana, endogenous neurotransmitters, and synthetic compounds. However, in this article, we use it to refer specifically to pharmaceutical drugs that are either:

Medical extracts from the cannabis plant, such as nabiximols (a patented formulation, trade name Sativex) or

Synthetic drugs that act on cannabinoid receptors, such as dronabinol and nabilone

Tetrahydrocannabinol (THC): The constituent of cannabis that by acting as an agonist on cannabinoid receptors is responsible for many of its psychoactive effects

Cannabinoid agonists: Cannabinoids that produce psychological effects similar to those produced by THC

Box 2: Approved medical uses for tetrahydrocannabinol and nabiximols

Controlling nausea and vomiting in cancer chemotherapy and radiotherapy (US)

Stimulating appetite in patients with AIDS related wasting (US)

Alleviating chronic neuropathic pain and muscle spasticity in multiple sclerosis (UK)

In the US, the smoking of cannabis has been advocated for medicinal purposes.¹ Since 1996, 20 US states and the District of Columbia have legislated (11 after citizen initiated referendums) to allow the medical use of cannabis, often to treat a much broader range of indications than those approved by the FDA or other regulators (see box 2).² In California, for example, doctors can recommend cannabis for any medical use if they believe that the patient may benefit.² These laws have created clinical conundrums for doctors in these US states.³

In the UK a cannabis based medical extract, nabiximols (see box 1)⁴ has been approved for “symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy on a named patient basis.”⁵

Should doctors consider prescribing cannabinoids for this indication? Should they consider prescribing nabiximols off label for other chronic conditions? What should doctors do if their patients disclose that they are smoking cannabis for medical purposes?

What is the evidence of uncertainty?

To examine the effectiveness and safety of medicinal use of cannabinoids we searched the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, and Embase without language restriction for studies published from 1 January 2008 to 3 October 2013. We checked references of reviews and included trials to identify additional studies. We considered indications for which cannabinoids have received regulatory approval in one or more countries (box 2), as well as use in chronic pain—the most common reported medical reason for use in the US.⁶ We used the Cochrane search strategy to identify systematic reviews and randomised controlled trials and included terms for cannabinoids and chronic neuropathic, chronic cancer pain, and non-cancer pain.

Antiemetic and appetite stimulating effects

In the 1970s and 1980s clinical trials compared the antiemetic effects of THC with a placebo or prochlorperazine, the drug then used to treat nausea in patients with cancer.^{1 7} These studies found that cannabinoids were more effective than placebo or prochlorperazine. However, the small size of most of the studies made it difficult to draw firm conclusions.^{8 9}

There are now newer, much more effective, anti-nausea drugs, such as ondansetron.^{1 10} These drugs have not been directly compared with cannabinoids,¹⁰ but indirect comparisons suggest that the newer drugs control nausea in a larger proportion of patients than THC does.^{1 10} Cannabinoids are thus not recommended as first line treatment for nausea in patients with cancer, although the cannabinoids may have a role as adjunctive treatments.^{1 11}

Dronabinol was registered in the US in 1992 on the basis of a small number of trials for stimulation of appetite in patients with AIDS related anorexia and weight loss.¹ A Cochrane review found no evidence for the efficacy and safety of cannabis and cannabinoids for either use in AIDS.¹² Treatment with antiretroviral drugs now prevents AIDS related wasting, making it unlikely that further trials of cannabinoids will be undertaken for this use.

Effects on muscle spasticity or neuropathic pain in multiple sclerosis

A 2011 systematic review of cannabinoids for treatment of chronic non-cancer pain identified four trials in people with multiple sclerosis but only reported the results narratively.¹³ Three small trials reported modest reductions in pain with nabiximols (two trials) or dronabinol (one trial).^{14 15 16} A fourth, larger trial (n=160) found that nabiximols had no advantage over placebo for pain, but that it did have greater effects on spasticity than placebo.¹⁷ Adverse events—including dizziness, dry mouth, and somnolence—were more common in the active treated groups.

A meta-analysis (without preceding systematic review) of this trial combined with two other trials sponsored by the same company reported significant benefits of nabiximols over placebo in a proportion of responders ($\geq 30\%$ reduction in spasticity; odds ratio 1.62, 95% confidence interval 1.15 to 2.28).^{18 19} There were, however, more withdrawals (11% v 3.6%) and more reports of at least one mild to moderate adverse event (79.3% v 55.8%), particularly dizziness,²⁰ in those receiving nabiximols. A subsequent narrative review of all these trials and nine additional ones was less positive. It concluded that, although nabiximols may have a role as an adjunctive treatment of muscle spasticity in multiple sclerosis, its efficacy and tolerability were poorly documented, and that further data were needed on its long term safety.²¹

An additional high quality randomised controlled trial (n=339), not included in this review, reported no significant difference in the proportion who responded ($\geq 30\%$ improvement in pain) between those receiving nabiximols (50%) versus placebo (45%). In a subsequent randomised withdrawal phase that involved 58 participants, there were more treatment failures among those in the placebo group (57% v 24%).²² Although a recent small

crossover trial (n=37) reported significantly greater improvement in spasticity and pain with cannabis versus placebo cigarettes, self selection bias (many participants had previously used cannabis) and unblinding of participants makes it impossible to draw firm conclusions.²³

Thus, the effectiveness of cannabinoids for the treatment of muscle spasticity or neuropathic pain in multiple sclerosis is unclear and any benefit is likely to be modest, while mild to moderate adverse events are common and long term safety has not been established.

Effects on other neuropathic pain

Systematic reviews of trials of cannabinoids in participants with other types of neuropathic pain have reported mixed results. For example, in a 2011 high quality systematic review that reported results qualitatively, seven of nine trials of people with other types of chronic neuropathic pain reported significantly greater analgesic effects for cannabinoids versus placebo, although the effect sizes were modest and trials were of short duration.¹³

A recent systematic review of drugs for neuropathic pain associated with spinal cord injury included one small (n=7) crossover trial that reported comparable benefits from dronabinol and diphenhydramine, an antihistamine that does not have pain relief properties but mimics some of the possible side effects of dronabinol.^{24,25} A systematic review of pharmacological treatment of HIV associated neuropathy that pooled data from two small placebo controlled trials of smoked cannabis reported a relative risk of at least a 30% improvement in pain of 2.38 (1.38 to 4.10) in favour of smoked cannabis.²⁶ Both trials, however, were at high risk of performance and detection bias, and one trial reported more adverse effects in the cannabis group, including two withdrawals (one for cannabis induced psychosis and intractable smoking related cough). One small (n=30) placebo controlled trial in people with painful diabetic neuropathy found that nabiximols did not reduce pain.²⁷ Another small trial (n=37) of nabilone, a synthetic cannabinoid, in refractory diabetic neuropathic pain, found a significant benefit compared with placebo in 70% of participants (26/37), who were deemed to be responders (achieved $\geq 30\%$ improvement in pain) to nabilone in an initial single arm blinded phase.²⁸

The effectiveness of cannabinoids for the treatment of other neuropathic pain has not been proved.

Effects on other chronic pain

One small low quality trial of nabiximols was included in a Cochrane review of neuromodulators for rheumatoid arthritis.²⁹ This trial reported a small significant benefit over placebo in pain—on a scale of 0-5, the mean between group difference was -0.72 (-1.31 to -0.13). Participants in the cannabinoid group were significantly more likely to experience an adverse event (mostly dizziness, dry mouth, and light headedness; number needed to harm 3, 3 to 13).²⁹

A recent systematic review of medicinal plants or related natural products for fibromyalgia identified two small trials of the efficacy of nabilone that were judged to be at low risk of

bias.³⁰ One trial found a significantly greater reduction in pain and anxiety with nabilone than with placebo.³¹ A second trial in people with fibromyalgia and chronic insomnia reported that nabilone and amitriptyline had similar effects on pain but that nabilone caused more adverse effects, particularly drowsiness and dizziness.³²

A crossover trial reported that nabilone reduced pain more than ibuprofen in people with medication overuse headache, although the between group difference was small and unlikely to be of clinical importance.³³

Thus, the effectiveness of cannabinoids in treating other chronic pain is unclear and any benefit is likely to be modest. Mild to moderate adverse events are often reported and long term safety has not been established.

Effects on cancer pain

A systematic review including 18 placebo controlled trials of cannabinoids for chronic cancer and non-cancer pain reported a clinically significant greater reduction in pain with cannabinoids from a pooled (fixed model) analysis that included four cancer trials and three trials for other chronic pain (standardised mean difference -0.61 (-0.37 to 0.84)).³⁴

However, the authors outlined serious sources of bias in the included trials that may have favoured the actively treated groups, including selection and attrition bias and perhaps inadequacy of participant blinding. The review also found that cannabinoids were more likely than placebo to be associated with adverse events linked to alterations in perception (odds ratio 4.51 , 3.0 to 6.66 ; 10 trials), motor function (3.93 , 2.83 to 5.47 ; 10 trials), and cognitive function (4.46 , 2.37 to 8.27 ; five trials).³⁴

Two additional trials of cannabinoids for people with cancer and an inadequate response to opioids, published after this review, also reported favourable efficacy results. However, in one trial higher doses of nabiximols (11-16 sprays/day), but not low (1-4 sprays/day) or medium doses (6-10 sprays/day), produced significantly more adverse events than placebo.³⁵ In the other trial, THC and cannabidiol worsened nausea and vomiting compared with placebo.³⁶

Thus, the effectiveness of cannabinoids for the treatment of chronic cancer pain remains unclear, although any benefit is likely to be modest. The available evidence indicates a risk of potentially serious adverse effects, including alterations in perception, motor function, and cognitive function.

Chronic adverse events

Box 3 outlines adverse effects of chronic recreational cannabis smoking identified from epidemiological studies.

Box 3: Adverse effects of chronic recreational cannabis smoking identified in epidemiological studies³⁷

Most probable adverse effects

- Cannabis dependence syndrome (around 1/10 users), the main features of which are compulsive use, tolerance of its effects, and withdrawal symptoms. Use may interfere with family, school, and work.
- Chronic bronchitis and impaired respiratory function in regular smokers
- Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders
- Impaired educational attainment in adolescents who use regularly
- Subtle cognitive impairment in those who use daily for a decade or more
- Possible adverse effects
 - Respiratory cancers
 - Behavioural disorders in children whose mothers used cannabis while pregnant
 - Depressive disorders, mania, and suicide
 - Increased likelihood of using other illicit drugs in adolescents

Is ongoing research likely to provide relevant evidence?

Box 4 outlines the key research questions in assessing the longer term efficacy and safety of nabiximols. We searched key trials registers including US ClinicalTrials.gov, EU Clinical Trials Registry, and Australian and New Zealand Clinical Trials Register. We identified 10 prospective studies of nabiximols but were unable to identify key studies that would provide important information in the near future. There is no guarantee that these studies will definitely answer the complex questions around effective pain control. However large scale, long term observational outcome studies or record linkage studies based on the use of nabiximols for medically approved indications, such as multiple sclerosis, may quantify the risks and benefits of long term use.³⁷

Box 4: Key research questions for medical use of cannabinoids

What are the long term efficacy and safety of nabiximols in patients with multiple sclerosis?

Population: Patients with multiple sclerosis and neuropathic pain and muscle spasm

Intervention: Long term use of oral nabiximols (over years)

Comparison: Antispasmodic agents and other agents used to treat neuropathic pain

Outcomes: Analgesic effects, development of dependence and other adverse outcomes, and discontinuation rates

Is nabiximols effective in treating chronic neuropathic pain?

Population: Patients with neuropathic pain of malignant or non-malignant origin

Intervention: Oral nabiximols

Comparison: Opioids, antiepileptic drugs, or antidepressants

Outcome: Effectiveness of analgesia and quality of life

What should we do in the light of the uncertainties?

What should clinicians advise patients who request a prescription for nabiximols or who want to use other cannabinoids for medical indications? If the product is legally available, then doctors are free to prescribe it for approved indications. If medical use is likely to be long term, patients should be warned that the adverse effects of long term use are unclear. Patients could also be advised of the adverse effects reported in long term recreational users, such as the development of dependence (box 3).

If a patient requests nabiximols for a non-approved or off-label indication, clinicians should avoid taking this medicolegal responsibility. If first line treatments have been ineffective or the patient insists on nabiximols, it may be sensible, when available, to refer the patient for specialist management of the condition, where a trial of cannabinoids might be undertaken.

Doctors are not legally able to prescribe cannabis (the plant product that is smoked) in any jurisdiction because it has not received regulatory approval (although doctors may “recommend” its use in some US states). Many doctors will be faced with patients using cannabis for complex symptoms of multiple chronic disabling conditions for which there are limited treatment options. Doctors should discuss, in a dispassionate and non-judgmental and supportive manner, the advisability or otherwise of using cannabis to palliate such symptoms. There is no clear evidence for effectiveness in treating pain, any benefits are likely to be modest, and there is no clear evidence that putative benefits outweigh possible harms.

When symptoms of cannabis dependence are elicited it is appropriate to discuss the wisdom of continued use in the context of the illness and the prognosis, and, if appropriate, to offer the patient support for withdrawal. Helping patients who wish to use cannabis for symptomatic relief to live as comfortably and productively as possible is an important and valuable goal of palliative and rehabilitation treatment.

Notes

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Footnotes

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the Cochrane Library. To suggest a topic, please email us at practice@bmj.com.

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Contributors: MF and WH jointly planned the paper, RB helped identify the literature to be included, read the papers cited, and all three authors jointly wrote the article and act as guarantors.

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