



TITLE: Cannabinoids for the Management of Neuropathic Pain: Review of Clinical Effectiveness

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CONTEXT AND POLICY ISSUES:

Neuropathic pain is a chronic and debilitating pain syndrome that affects an estimated 3% of the population.¹ Neuropathic pain arises from damage to the nervous system (brain, spinal cord, or peripheral nerves)² caused by diseases such as diabetes, cancer, viral infections (HIV, Varicella Zoster), trigeminal neuralgia, and spinal cord injury.¹ The etiology of neuropathic pain is not entirely clear, but is related to a blockage of nerve conduction (peripheral mechanism) and sensitization to pain (central mechanism).¹ This blockage of nerve conduction is associated with numbness and tingling in the affected area and pain that can be varied in its characteristics.¹ Neuropathic pain can be continuous or can be transient and have a burning, shooting, or shock-like quality.¹ Neuropathic pain can occur spontaneously or in response to a painful or non-painful stimulus (e.g., a breeze blowing on the skin).¹

Neuropathic pain often does not respond well to pharmacotherapy and medications used in its treatment often have adverse effect profiles that make it difficult to achieve maximal therapeutic dosing, resulting in limited symptomatic relief.² Tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, anticonvulsants (pregabalin, gabapentin, carbamazepine, phenytoin), topical lidocaine, and opioids are all used in the management of neuropathic pain.³

Cannabinoids (a term that refers to all natural and synthetic ligands for the cannabinoid receptor) have also been studied in the treatment of neuropathic pain.⁴ Some cannabinoid receptors are centrally located and suppress pain when bound by a ligand.⁴ There are three cannabinoids on the market in Canada available at present in addition to medical marijuana (phytocannabinoids).⁴ Nabilone (marketed under the name Cesamet) and delta-9-tetrahydrocannabinol (dronabinol; marketed under the name Marinol) are orally administered cannabinoids and are approved for use as antiemetics in patients undergoing chemotherapy.^{5,6} Dronabinol is also approved for the treatment of anorexia and weight loss associated with AIDS.⁶ A combination of delta-9-tetrahydrocannabinol and cannabidiol (THC:CBD); marketed under the brand name Sativex) is available as a buccal spray and is approved for use as an

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adjunctive treatment of neuropathic pain in multiple sclerosis (MS) and for moderate to severe pain in adults with advanced cancer who are already treated with the maximally tolerated dose of strong opioid.⁷

This report will review the evidence of effectiveness of cannabinoids in the management of neuropathic pain, which could be used in decision-making at the health-care system level and in individual patient management.

RESEARCH QUESTION:

What is the evidence regarding the clinical effectiveness of cannabinoids for the management of neuropathic pain?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including Medline, Embase, The Cochrane Library (Issue 6, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and June 16, 2010. No filters were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS:

Seven relevant randomized controlled trials were identified from the literature search.⁸⁻¹⁴ Six of the seven studies compared a cannabinoid or cannabis to placebo in the treatment of neuropathic pain.^{8-10,12-14} One study compared nabilone to a narcotic analgesic.¹¹

Randomized Controlled Trials

Delta-9-tetrahydrocannabinol and cannabidiol (THC:CBD)

A 2010 randomized, placebo-controlled trial assessed the efficacy of THC:CBD as add-on therapy for the management of peripheral neuropathy in individuals with diabetes.⁸ The study enrolled 30 patients with chronic painful peripheral neuropathy for at least 6 months with stable glycemic control (A1C <11%). As well, patients had to be currently treated with tricyclic antidepressants and still experiencing persistent pain. The study setting was not described. THC:CBD and placebo were administered sublingually as pump action sprays. Patients were permitted to continue their other medications for peripheral neuropathy. The study lasted 12 weeks in total, which consisted of a 2-week titration phase, followed by 10 weeks of maintenance. Pain was assessed using a 100-mm visual analog scale (VAS) which was the primary outcome measure. Quality of life was a secondary outcome and was measured with the McGill Pain and QOL scale, the SF-36, and the EQ-5D.

Total pain scores improved in both groups from baseline to follow-up and the mean change did not differ between groups ($p=0.40$). There were no significant differences in secondary outcome measures. From these results, the authors concluded that THC:CBD was no more efficacious than placebo in painful peripheral neuropathy. It was not clear whether this sample would be

representative of the broader population with diabetes and peripheral neuropathy. Further, it is not known if the results would be generalizable to patients with neuropathy secondary to other causes. The sample size may have limited the ability to detect statistically significant differences between groups.

A 2007, randomized, double-blind, placebo-controlled parallel group study assessed the efficacy and adverse effects of THC:CBD in 125 patients with neuropathic pain and allodynia (painful response to a stimulus that does not normally elicit pain).¹² The study took place at five centres in the United Kingdom and Belgium, but the setting was not described in greater detail. The study had extensive inclusion (a minimum score on a pain rating scale, stable medication regimen, duration of pain of at least six months) and exclusion criteria (such as psychiatric disorders, severe chronic conditions, history of substance abuse, cannabinoid use within seven days of randomization). Patients were randomized to THC:CBD (n=63) or placebo (n=62). The dosage of the study medications was individualized under supervision, with the maximum dose being eight sprays per three-hour period, up to a maximum of 48 sprays per 24 hours. Patients were permitted to continue stable analgesic regimens. The primary outcome was the change from baseline in neuropathic pain intensity on a 10-point numeric rating scale (NRS). Secondary outcome measures were the Neuropathic Pain Scale (NPS), tests for mechanical allodynia, sleep disturbance, the Pain Disability Index (PDI), the Patient Global Impression of Change (PGIC), and the General Health Questionnaire (GHQ-12). The study duration was five weeks. The analysis was adjusted for baseline severity of pain and treatment centre.

At the end of follow-up, the average reduction in pain intensity scores was greater in the THC:CBD group than in the placebo group (-0.96 point difference; 95% CI: -1.59 to -0.32; p = 0.004). Secondary outcome measures also favoured THC:CBD over placebo and all differences were statistically significant (NPS score, sleep, allodynia, PDI and PGIC). The authors concluded that THC:CBD had a positive effect on neuropathic pain with allodynia, when used as an add-on therapy to existing analgesics.

A 2005 randomized, double-blind, placebo-controlled trial assessed the efficacy, safety, and tolerability of THC:CBD in 66 patients with MS and neuropathic pain.¹⁴ This five-week study was conducted in a clinical trials unit in the United Kingdom. Patients with MS for at least six months and neuropathic pain for at least three months were eligible to be included in the study and were randomized to THC:CBD (n=34) or placebo (n=32). Patients were excluded if they had spasticity or painless spasms alone, a history of major psychiatric disorders, a severe comorbidity, seizures, history or suspicion of substance abuse, severe pain that was not neuropathic in nature, the presence of another medical condition associated with peripheral neuropathic pain, were pregnant or lactating, taking levodopa, or had known or suspected hypersensitivity to cannabinoids. Patients could self-titrate the study medications to a maximum of 48 sprays in 24 hours. Stable neuropathic pain medications were continued throughout the study. The primary outcome measure was pain severity on an 11-point numeric rating scale. Other outcome measures included an 11-point rating of sleep disturbance related to neuropathic pain, the Neuropathic Pain Scale, measures of mood and disability, and the patient's global rating of change in pain.

The difference in treatment effect for the severity of pain measure was -1.25 (95% CI: -2.11 to -0.39; p=0.005) favouring THC:CBD over placebo. For the Neuropathic Pain Scale, the difference was -6.58 (95% CI: -12.97 to -0.19; p=0.044) in favour of THC:CBD. Measures of

sleep disturbance also favoured THC:CBD over placebo (mean difference = -1.39 ; 95% CI: -2.27 to -0.50; $p = 0.003$). For the rating of change, measures of mood and disability rating did not differ between THC:CBD and placebo. The authors concluded that THC:CBD was effective in reducing pain and sleep disturbance in patients with MS and neuropathic pain. The results of this study may not be generalizable to different patient groups or to other cannabinoids.

Of the 66 patients originally enrolled in this study, 28 completed a two-year uncontrolled, open-label study.¹⁵ In the final week of treatment of the 2-year follow-up, the mean pain score in the final week of treatment was 2.9, compared to 3.8 at the end of the initial RCT. Pain was measured on an 11-point scale with anchors of 0 (no pain) and 10 (worst imaginable pain). Approximately 92% of patients experienced one or more adverse effect, the most common of which were nausea and dizziness. The authors concluded that in patients with MS and neuropathic pain, THC:CBD was effective, with no evidence of tolerance.

Smoked Cannabis

A 2009 double-blind, placebo controlled, randomized study assessed the usefulness and dosing range of smoked medicinal cannabis for the treatment of refractory neuropathic pain in distal sensory polyneuropathy (DSPN) in 34 patients with HIV.⁹ The study was set in an outpatient research clinic of a hospital in San Diego, CA. This was a seven week cross-over trial involving a single group of patients with documented HIV who had neuropathic pain that was unresponsive to treatment to two or more trials of analgesics. As well, patients had to score at least five on a pain scale called the Descriptor Differential Scale (DDS), which ranges in value from 0 to 20. Patients with current substance use disorders, histories of dependence on cannabis, psychosis with cannabinoids, and intolerance to cannabinoids were excluded, as were those using an approved cannabinoid medication or whose toxicology screen identified cannabinoids or recreational drugs such as amphetamine or cocaine. Those with serious medical conditions other than HIV were also excluded.

Patients were permitted to continue with the analgesics they were taking prior to study initiation. Following a one-week washout period, patients were treated for five days with smoked active or placebo cannabis. This was followed by a two-week washout period and then five days of smoked active or placebo cannabis (the cross-over treatment), followed by a final two week washout period. The treatment order was randomly assigned. The National Institute on Drug Abuse supplied the active and placebo cannabis, with the strengths of active cannabis ranging from 1% to 8% D-9-THC concentration by weight to allow for dosage titration. Patients smoked active or placebo cannabis at the clinic in four daily smoking sessions that were 90 minutes to 12 hours apart while being supervised by a study nurse. The primary outcome measure of the study was pain measured by the DDS and mood and functioning were secondary outcomes.

A total of 28 patients completed the study, all of whom were male. The median difference in pain reduction between placebo and cannabis was 3.3 points on the DDS ($p=.016$) in favour of cannabis, which was an effect size of 0.60. A VAS was used as a secondary pain measure and demonstrated a median decrease of 17 points (range - 58 to 52) with cannabis compared to a decrease of 4 points (range -56 to 28) for placebo ($p<0.001$). Differences in secondary outcomes were reported as not significant, but the data were not shown. The authors concluded that smoked cannabis was generally effective for relieving pain associated with HIV DSPN when given as an add-on therapy. One limitation to this study was an inability to maintain the double-

blind design; over 90% of patients correctly guessed their treatments during the five day treatment with active cannabis. Generalizability of this study could be limited by its sample size. As well, the results might not be generalizable to neuropathic pain attributable to other underlying diseases, patients with substance use disorders, other excluded conditions, or to females with HIV.

A 2008 randomized, double-blinded, placebo controlled, crossover study assessed whether smoking cannabis produced dose-dependent relief of spontaneous and evoked pain in 38 patients with neuropathic pain.¹⁰ The study was set in two hospital-based pain clinics in California in a university-based hospital and a veterans' affairs hospital. Patients with neuropathic pain and previous exposure to cannabis were enrolled. However, it was required that all participants discontinue smoking cannabis or taking approved cannabinoids for 30 days before the study began. Those with severe major depressive disorder were excluded, as were those with uncontrolled hypertension, cardiovascular disease, chronic pulmonary disease, and active substance abuse. Patients were instructed to continue their current medications, with the aforementioned exception of cannabis and cannabinoids.

Treatments were assigned randomly and all patients received each treatment once for a total of three study sessions per patients. The treatments were high-dose cannabis (7% D-9-THC), low-dose cannabis (D-9-THC), and placebo cannabis. The National Institute on Drug Abuse supplied the active and placebo cannabis, with the strengths of active cannabis ranging from 3% to 7% D-9-THC concentration by weight. The smoking occurred under a fume hood that had constant ventilation using a cued-puff procedure. The dosage (nine puffs) was administered over a two hour period. Outcomes were measured three hours after the session and included pain measured on a 100-mm VAS and expressed as the pain intensity reduction per minute. Secondary outcome measures included pain unpleasantness measured on a 100-mm VAS, a 7-point patient global impression of change scale, an 11-point neuropathic pain scale, and a mood and a neurocognitive assessment.

A total of 32 patients completed the study sessions. The pain intensity reduction per minute (a measure of pain relief that attempts to include the effect of time) was as follows:

- Placebo: - 0.0040 (95% CI: -0.0060 to -0.0021)
- 3.5% D-9-THC: - 0.0085 (95% CI: -0.010 to -0.0066; $p < 0.01$ compared to placebo)
- 7.0% D-9-THC: - 0.0085 (95% CI: -0.010 to -0.0065; $p < 0.01$ compared to placebo)

Results also indicated that pain was more tolerable at higher cumulative doses of cannabis compared to placebo and that the global impression of change was greater for both cannabis groups than placebo. Differences on the pain intensity reduction and global impression of change were not statistically significantly different for the two dosages of 9-D-THC. For the neuropathic pain scale, cannabis improved sharp, burning, aching, sensitive, superficial, and deep pain ($p < 0.001$ for all comparisons) to a greater extent than placebo with no additional benefit of the 7.0% dosage compared to the 3.5% dosage. For most mood measures, there were no changes with cannabis use. Calmness was greater with the 3.5% dosage and placebo ($p = 0.03$), but not with the 7% dosage ($p = 0.60$). The 7% dosage group had more pronounced cognitive impairment on the neurocognitive tests than the 3.5% and placebo groups. The authors concluded that the study provided evidence that cannabis may be an effective alternative in the treatment of neuropathic pain for patients who fail on other treatments due to

lack of efficacy or adverse effects. Limitations to this study include its duration (a single treatment of each dose or placebo) which did not allow any longer-term effects to be assessed. Approximately 58% of patients had complex regional pain syndrome. It is not clear if the observed results would be generalizable to other causes of neuropathic pain.

A 2007 randomized placebo-controlled trial assessed the efficacy of smoked cannabis on neuropathic pain in 55 patients with HIV from a research clinic in California.¹³ Patients with HIV infection and sensory neuropathy with an average pain score of 30 mm on a 100 mm VAS were included. Patients had to be in stable health, not currently abusing substances, with stable medication regimens, and have a history of smoking cannabis. Patients with a family history of polyneuropathy, neuropathy unrelated to HIV, or using isoniazid, dapsone, or metronidazole within the past eight weeks prior to enrollment were excluded. Patients were randomized to smoked cannabis (3.56% 9-D-THC) (n=27) or identical placebo cigarettes (n=28) three times daily for 5 days. The National Institute on Drug Abuse provided the study medications. The study medications were smoked under supervision using a standardized technique up to three times daily. Primary outcome measures included the chronic pain rating on a 100 mm VAS and the percentage of patients achieving greater than 30% reduction in pain intensity. The immediate reduction in neuropathic pain was the secondary outcome measure.

Approximately 52% of patients in the cannabis group and 24% of patients in the placebo group had a greater than 30% reduction in pain intensity (difference 28%; 95% CI: 2% to 54%, $p = 0.04$). The median reduction in neuropathic pain VAS was 34% in the cannabis group and 17% in the placebo group (median difference 18%; $p = 0.03$). A 72% reduction in pain rating was observed in the cannabis group compared to 15% in the placebo group ($p < 0.001$) with the first cigarette, while on day five, the last cigarette decreased the pain rating by 51% in the cannabis group and 5% in the placebo group ($p < 0.001$). The authors concluded that smoked cannabis was effective in treating neuropathic pain from HIV-associated sensory neuropathy. It is not clear if the results of this study would be generalizable to other causes of neuropathy.

Nabilone

A 2008 randomized, double-blind, crossover trial compared the safety and efficacy of nabilone (n=48) and dihydrocodeine (n=48) for chronic neuropathic pain.¹¹ The study was conducted in three hospital-based outpatient chronic pain units in the United Kingdom. Patients were included if they had neuropathic pain with a clear history of the underlying cause and had a mean pain score greater than 40 mm on a 100 mm VAS. Patients were excluded if they were taking any cannabinoid preparation, antipsychotics, benzodiazepines, or monoamine oxidase inhibitors; had ongoing legal action related to neuropathic pain; or had severe hepatic or renal disease, epilepsy, bipolar disorder, psychosis, or a history of substance misuse. Patients were permitted to continue any stable analgesic except dihydrocodeine. Study medications were titrated up to 240 mg of dihydrocodeine and 2 mg of nabilone. There were three trial periods: the first six-week treatment period, a two-week washout period, and a second six-week treatment period. The primary outcome measure of the study was pain control on a 100 mm VAS and secondary outcomes included anxiety and depression (determined from the Hospital Anxiety and Depression scale - HADS), health-related quality of life measured using the SF-36 (an eight domain measure - Physical functioning; Social functioning; Role, physical; Role, emotional; Mental health; Vitality; Bodily pain; and General health), and the average number of hours of sleep each night. Of the 96 patients randomized, 73 had data available for the analysis.

The pain scores on the VAS favoured dihydrocodeine over nabilone, with a difference of 6.0 mm (95% CI 1.4 to 10.5; $p=0.01$). The authors stated that this difference was not clinically relevant at a threshold 10 mm. The bodily pain domain of the SF-36 also favoured dihydrocodeine (mean difference of -5.2 , 95% CI -10.1 to -0.4 , $p=0.03$). The Role, physical domain of the SF-36 favoured nabilone (mean difference of 8.9, 95% CI 1.1 to 16.7, $p=0.03$). No other differences in sleep or SF-36 domain and HADS scores were observed. In terms of adverse effects, “sickness” was more common with nabilone, and tiredness and nightmares were more common with dihydrocodeine. The authors concluded that pain relief with dihydrocodeine was superior to nabilone, with slightly less adverse effects. The generalizability of this study could be limited by the incomplete follow-up and dihydrocodeine not being available in Canada. As well, the exclusion of patients with psychiatric and substance abuse disorders could limit the generalizability to these populations.

Limitations

Seven relevant RCTs were identified from the search strategy. Studies generally enrolled patients whose pain exceeded a minimum threshold and who failed on other analgesics. The studies tended to have numerous exclusion criteria, in particular psychiatric disorders and substance abuse disorders. These factors could limit the generalizability of the results to patients with less severe pain or comorbidities. While the efficacy of smoked cannabis was assessed in three RCTs, two of the three studies were in populations with HIV. It is not clear whether the results could be generalized to other patient groups. The studies of smoked cannabis could also potentially be biased by difficulties in blinding treatment status due to its psychoactive effects. The longest duration of treatment in the included RCTs was five weeks. Thus, it is not clear if the observed effects on pain relief would be observed longer-term, although one open-label, uncontrolled study in patients with MS suggested that the analgesic effect could last up to two years. No study assessed the efficacy of dronabinol in neuropathic pain and one study assessed the effect of nabilone. As such, data on the efficacy of these agents in managing neuropathic pain is sparse. All studies, with the exception of one, compared the effects of the cannabinoid to placebo, so data on comparative efficacy to other treatments for neuropathic pain are lacking. Further, where a treatment effect was observed, the clinical relevance of the magnitude of effect was generally not described. One study suggested a 10mm difference on the VAS to be clinically relevant, but this was the only benchmark provided. The efficacy of cannabinoids was assessed as add on therapy. Cannabinoids monotherapy for the treatment of neuropathic pain was not assessed in any of the included studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In two five-week RCTs, THC:CBD was more effective than placebo when added to existing therapy for the management of neuropathic pain associated with MS and in patients with neuropathic pain stemming from mixed etiologies. In a longer study (12 weeks) in patients with diabetic neuropathy, there was no difference between THC:CBD and placebo in the management of neuropathic pain. This may suggest that THC:CBD is either not effective in diabetic neuropathy or that the analgesic effects of THC:CBD diminished with longer duration of treatment in this population.

One study reported that smoked cannabis was superior to placebo in reducing neuropathic pain associated with HIV when assessed after five days of treatment. Another study that assessed

the effect of smoked cannabis on neuropathic pain stemming from mixed etiologies suggested that cannabis was superior to placebo, but that there was a ceiling effect with the dosage, meaning that the higher dosage (7% 9-D-THC) was no more effective than the lower dosage (3.5% 9-D-THC). This was based, however, upon an evaluation of a single dose of each concentration of D-9-THC and placebo.

One study of nabilone in chronic neuropathic pain suggested that pain relief with the narcotic analgesic dihydrocodeine was superior to nabilone. This was the only comparative study of active treatments, so further research would be needed to make any conclusions regarding relative efficacy of nabilone or other cannabinoids.

Overall, the limited evidence suggests that cannabinoids may provide pain relief in patients with HIV or MS who have neuropathic pain when used as add on therapy. It is not clear if this benefit would be maintained longer-term. No benefit was observed in diabetic neuropathy and pain relief with nabilone was inferior to a narcotic analgesic. These points may be considered when making formulary decisions about the use of cannabinoids in neuropathic pain.

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