therapeutics letter
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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

# Cannabinoids for Chronic Pain


Canada's parliament legalized the recreational use of herbal cannabis (marijuana) in October 2018. The well-publicized limitations of clinical research and well-recognized side effects such as cannabis intoxication have not deterred people from seeking out and using herbal cannabis for chronic pain in increasing numbers. This is occurring with or without a physician's authorization.[1] In fact, half of Canadians reporting a medical use of herbal cannabis used it for pain relief.[2]

Adult patients in Canada still require a physician's '*authorization*' to legally access cannabis from a licensed producer of cannabis for medical purposes. Facilitating access to any cannabinoid (pharmaceutical or herbal) by a physician in British Columbia is considered the equivalent of a formal prescription by the College of Physicians and Surgeons of British Columbia.[3]

A recent communication from Harvard University provides this useful advice for physicians:

> "*Whether you are pro, neutral, or against medical marijuana, patients are embracing it, and although we don't have rigorous studies and 'gold standard' proof of the benefits and risks of medical marijuana, we need to learn about it, be open-minded, and above all, be non-judgmental. Otherwise, our patients will seek out other, less reliable sources of information; they will continue to use it, they just won't tell us, and there will be that much less trust and strength in our doctor-patient relationship.*"[4]

This Therapeutics Letter provides a brief overview of pharmaceutical cannabinoids and herbal cannabis and the best available evidence for their use in the management of chronic pain.

## Pharmaceutical cannabinoids approved for chronic pain management

Pharmaceutical cannabinoids are manufactured drug products with a consistent content and delivery mechanism. Nabiximols (Sativex) and nabilone (Cesamet, generics) are two pharmaceutical cannabinoids approved by Health Canada to date on the basis of clinical trial submissions. Only nabiximols has an approved indication for chronic pain in two clinical circumstances: neuropathic pain in multiple sclerosis, and advanced cancer pain despite the use of strong opioid therapy.[5]

## Pharmaceutical and herbal cannabinoids not formally approved for chronic pain management

Pharmaceutical cannabinoids and herbal cannabis are used for chronic pain in many clinical settings without formal Health Canada approval and thus represent an off-label use. Unfortunately, bias is pervasive throughout the medical cannabinoid literature, including in randomized controlled trials (RCTs). Even within an RCT study design, major challenges remain in interpreting the findings due to the difficulty in maintaining blinding and the great variability of herbal cannabis products.

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Herbal cannabis is a complex mixture of many ingredients. Fortunately, producers are currently required to report on the composition of the major active ingredients, which are pharmacologically very different: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). For example, a recent World Health Organization pre-review concluded: "CBD exhibits no effects indicative of any abuse or dependence potential… CBD is generally well tolerated with a good safety profile."[6] THC, on the other hand, is responsible for the intoxicating effects and the potential harms associated with that.

At the present time we are hampered by the lack of experimental evidence about product composition, dose, appropriate outcomes to measure benefit, as well as short and long-term adverse effects and adverse interactions with other drugs. There is a great need for more research. Future trials need to use fixed dose product composition and measure real world benefits and harms over suitably long durations.

## Neuropathic pain

### Benefits:

Two systematic reviews, a Cochrane review[7] published in the Cochrane Database of Systematic Reviews in March 2018 and a systematic review of systematic reviews[8] published in the Canadian Family Physician in February 2018, best summarize the available clinical trial evidence. We have selected these two reviews, because they are written by non-conflicted authors and are up-to-date, comprehensive and relevant to the Canadian population. Herbal cannabis has less evidence than pharmaceutical cannabinoids. In the Cochrane review, for example, only two of the 16 studies evaluated herbal cannabis (one was an RCT from Canada[9] using a product from a Canadian producer).

The Cochrane review reported that cannabis-based medicines increased the number of people achieving 50% or greater pain relief compared with placebo; number needed to treat (NNT) = 20 (95% CI 11 to 100).[7] The Canadian review (15 RCTs) reported that more patients taking cannabinoids attained at least a 30% pain reduction: NNT = 11.[8]

### Harms:

In the Cochrane review[7] withdrawals due to adverse effects were increased with cannabis; number needed to harm (NNH) = 25 (16 to 50). In the Canadian review[8] adverse effects caused more patients to stop treatment, NNH ranged from 8 to 22. Individual adverse events were very common, including dizziness (NNH = 5), sedation (NNH = 5), confusion (NNH = 15), and dissociation (NNH = 20). "Feeling high" was reported in 35% to 70% of users.

### Bottom line from the Cochrane review:

**"There is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain." [7]**

## Conclusions

- Health care providers need to be knowledgeable and non-judgmental when informing patients about cannabinoids.
- The complexity of cannabinoids as a therapy makes research particularly difficult.
- **At the present time we lack good evidence that any cannabis-derived product works for chronic pain.**
- Future trials need to use fixed dose product composition and assess real world benefits and harms over suitably long durations.

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The draft of this Therapeutics Letter was submitted for review to 130 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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