Consideration of cannabinoids in the treatment of Diabetic Peripheral Neuropathic Pain

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About the Author

Dr. Taylor Lougheed is a family, emergency, sport, and cannabinoid physician living and practicing in North Bay, Ontario. He completed his medical school training at Queen's University, his family medicine residency at the University of Toronto, and his emergency medicine enhanced skills residency at the University of Ottawa. He is an experienced cannabinoid physician with a consult-based practice that focuses on complex refractory conditions in all ages and has given over 100 cannabinoid based academic talks. Dr. Lougheed is an Assistant Professor at the Northern Ontario School of Medicine and the University of Ottawa.

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Introduction

Diabetic Peripheral Neuropathic Pain (DPNP) is a leading complication of diabetes that can have marked impacts on quality of life,[1] may lead to increased depressive symptoms,[2] and can be difficult to treat due to medication side effects.[3] As a result, there has been growing interest in exploring adjunctive treatment options for chronic neuropathic pain, including medical cannabinoids. While the pathogenesis of DPNP is not fully understood, there is evidence that persistent hyperglycemia contributes to a number of processes leading to vascular damage, increased oxidative stress, and release of free radicals and pro-inflammatory molecules[4,5]—all of which may lead to DPNP symptoms, including pain.

Cannabinoids and the Endocannabinoid System

The endocannabinoid system (ECS) is ubiquitous in the human body and has been linked to a range of system pathways, including those implicated in seizures, mood, nausea, sleep, and pain. Cannabinoid receptors, such as the CB1 receptor, are highly present in the central nervous system where they are the most common form of G-protein coupled receptor, as well as the peripheral nervous system where they are commonly found at sympathetic nerve terminals.[6] Both the location and density of receptors make the ECS an interesting potential therapeutic target for treating neuropathic pain.

The Cannabis sativa plant is the best-known source of cannabinoid chemicals, including the two most common: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has a longstanding tradition in various cultures of medicinal and spiritual use, and more broadly as a recreational substance with psychoactive effects. Adverse effects may include tachycardia, hypotension, fatigue, changes in appetite, anxiety, psychosis, and impaired judgement and coordination. CBD itself does not have recreational psychoactive effects and has recently been promoted as having a wide range of potential clinical uses, including anti-inflammatory and antioxidant properties.[7]

While CBD is generally well tolerated, some common side effects may include fatigue or sedation, diarrhea, and changes in appetite or weight.[8] Both THC and CBD are metabolized by the cytochrome P450, leading to consideration of potential drug interactions.

Medical Cannabinoids in Canada

In Canada, medical cannabinoids can be divided into prescription-based and authorization-based (Table 1). Cannabis has been officially legal in Canada

Prescription-based	THC:CBD content	Health Canada approved application
Nabilone	Synthetic THC available in 0.25mg, 0.5mg and 1 mg capsules	Chemotherapy-induced nausea and vomiting
Nabiximols	Plant-derived oromucosal spray with 2.7 mg THC and 2.5 mg CBD per spray	MS-related spasticity, secondarily for adjunctive symptomatic treatment of neuropathic pain in MS; cancer-related pain
Authorization-based	**THC:CBD content**	**Health Canada approved application**
Herbal cannabis, including gel capsules, edible oils, topical oils, vape products	Variable ratios. Common oil formats include: • CBD dominant 1:20 • Balanced 1:1 • THC dominant 20:0	None; medical cannabis is regulated, but has no specific approved application

Table 1: Legal forms of medical cannabinoids in Canada

for medical purposes since 2001, and for recreational use since 2018.

Prescription-based medical cannabinoids are those that have a drug identification number (DIN), require a prescription, and are dispensed at a pharmacy. These products undergo Health Canada's drug approval process.

Authorization-based products are covered by the Cannabis Act, but do not have a DIN and therefore cannot be prescribed but are instead authorized. The patient is then registered with a licensed producer (a company legally licensed to produce and sell plant-derived medical cannabis products). The products are ordered online and delivered directly to the patient via the postal system. These products may include dried herbal products intended for combustion and inhalational use, vape products, oils intended for ingestion or topical application, gel capsules, and a variety of edible products, and are regulated by Health Canada but not specifically approved for any indication. Due to the wide heterogeneity of strains and products, coupled with historic regulatory and legal restrictions, there is a paucity of randomized controlled clinical trials using medical cannabinoids.

Medical Cannabinoids and Neuropathic Pain

Historically, cannabinoids have not routinely been recommended for the treatment of neuropathic pain due issues of legality, lack of evidence or concerns about risk of use. Within the last decade there have been multiple organizations and societies that have reviewed the evolving literature and have published updated guidelines positioning cannabinoids as a third-line treatment for chronic neuropathic pain (Table 2).

Organization	Cannabinoid Role
Canadian Pain Society, 2014[9]	3rd line
European Pain Federation (EFIC), 2018[10]	3rd line
German Pain Society, 2019[11]	3rd line
International Society for the Study of Pain (IASP) French Chapter, 2020[12]	Inconclusive due to lack of high-quality evidence.
American Academy of Neurology, 2022[13]	Limited comment on nabilone: "probably more likely than placebo to improve pain."

Table 2: Summary of international societies/organizations and their recent cannabinoid recommendations for neuropathic pain

The reviews leading to these updated guidelines generally assessed a small pool of existing higher-quality clinical studies, often with the use of prescription-based medical cannabinoids. While there is a wealth of animal-based studies showing promising cannabinoid efficacy for neuropathic pain, there remain a limited number of human clinical studies. Below is a summary of several recent studies not captured in some of the earlier reviews.

- A small trial of 17 patients with chronic lumbar radicular pain was published in 2018 that randomized the patients to receive either THC-based oil or placebo oil. The THC group experienced a statistically significant improvement in perceived pain.[14]
- A small trial of 29 patients with peripheral neuropathy was published in 2020 and randomized patients to CBD-based topical oil or placebo with crossover possible at 4 weeks. The CBD group demonstrated statistically significant reductions in intense and sharp pain, but not in deep pain. No adverse effects were experienced during the study period.[15]
- Two real-world reviews of the German Pain e-Registry resulted in publications in 2019 and 2022:
  - A 12-week open-label, real-world review of 800 patients treated with a balanced THC:CBD oromucosal spray as an adjunctive treatment for refractory and severe chronic pain. The conclusion was that the treatment was well tolerated and effective, particularly for neuropathic pain.[16]
  - A retrospective real-world comparison of the effectiveness of an oral THC-based treatment versus a balanced THC:CBD based oromucosal treatment with 337 patients in each arm. The study concluded that both were effective, but that the balanced THC:CBD appeared to be more effective and better tolerated.[17]

Undoubtedly a need remains for larger high-quality studies that can address gaps in knowledge relating to efficacy, strain/product selection, patient selection, dosing, and long-term safety.

Practical Considerations for Authorizing

The decision to move forward with cannabinoid-based treatment (prescriptions or authorizations) should be made on a patient-by-patient basis with shared decision making and consideration of patients' personal health characteristics, potential medication interactions, adverse effect risks, and severity of symptoms and response to initial treatments, as well as clinician comfort and expertise.

Authorization

The two components required for a patient to order medical cannabis products are the authorization provided by the clinician and the patient registering directly with a licensed producer. The authorization must include the patient's name and date of birth; the quantity of dried herbal cannabis equivalent per day (which is treated as a monthly quota for ordering purposes); the duration of the authorization (up to a maximum of 12 months) and the clinician's name, medical license number, business address, and signature. Many provincial regulatory bodies recommend including a THC limit on authorizations.

Titration

Historically, titration of medical cannabis has been clinician-dependent, but as clinical experience and research in this area have evolved, there has been a growing move toward expert, research-informed consensus guidelines. An example of these are the recently published recommendations for the dosing of medical cannabis to treat chronic pain which were developed by an international team via a modified Delphi method.[18] This has been modified to provide simple step-wise dosing considerations (Figure 1).

Delivery Options

Historically, only dried herbal cannabis products were available for legal sale in Canada. Over time, there have been the development and approval of a wide range of products including topical options, edibles and orally ingested oils or capsules, and vapes. While pharmacokinetic and pharmacodynamic data is not routinely available for each product, there are some general considerations with each option (Table 3).

Delivery Options
Topical creams and oils are becoming an increasingly viable option and may help reduce systemic side effects. A historical concern has been that the lipophilic nature of cannabinoids reduces transdermal absorption and cost-effectiveness.
Orally ingested oils or gel capsules are commonly recommended for chronic symptoms due to their ease of dosing and longer duration of action. They are also more accessible to patients who do not have a history of smoking or vaping.
Inhalational options such as smoking or vaping allow for rapid absorption and easy titration by patients, but shorter duration and higher fluctuations in blood cannabinoid levels. While an option for certain patients, notably with acute pain flares requiring rapid treatment, they are less frequently recommended in the context of chronic symptoms. Smoking and other combustion methods are not recommended due to health risks.

Table 3: General considerations for various delivery mechanisms

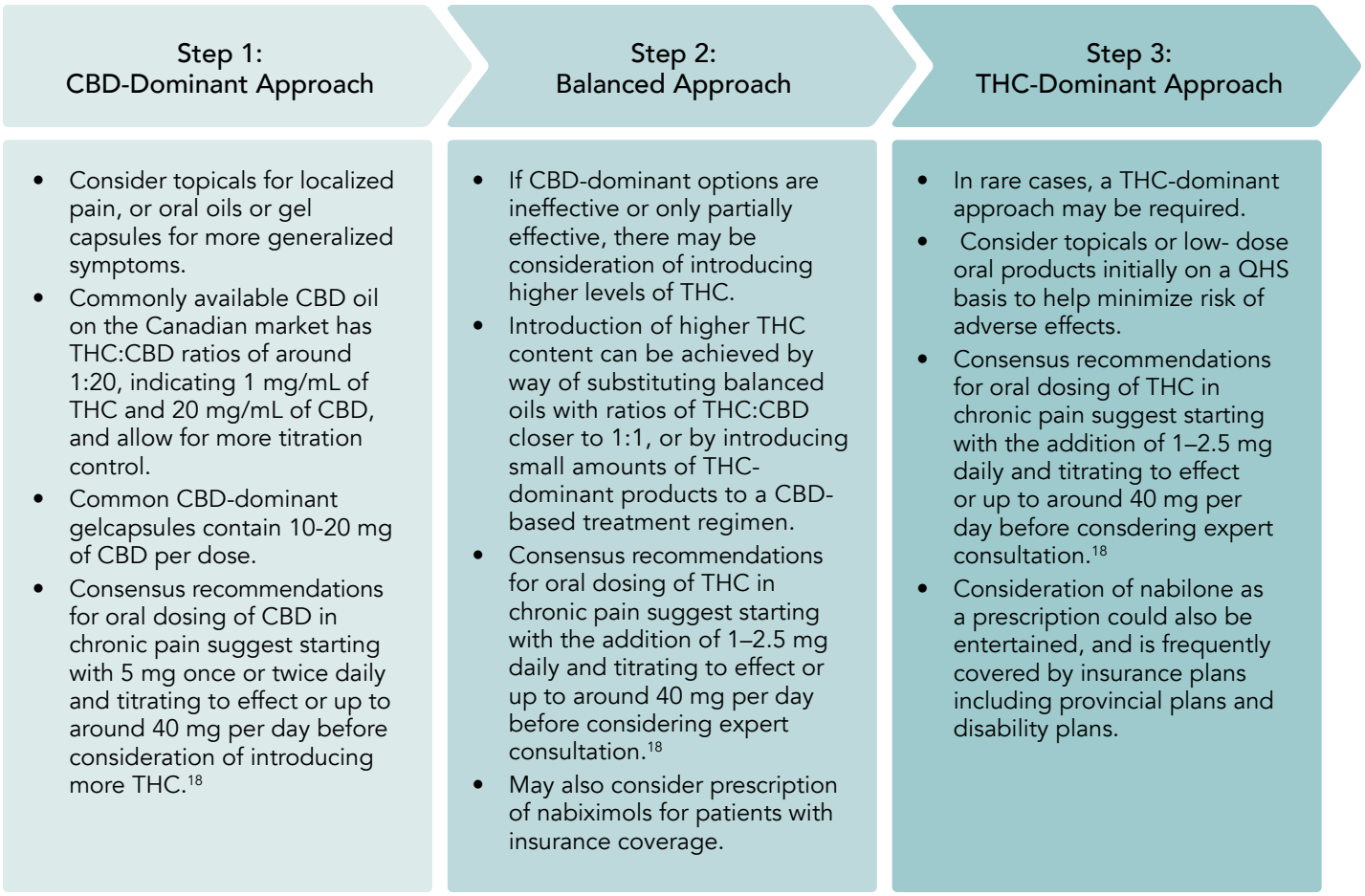

Figure 1: Step-wise dosing considerations (Modified from Bhaskar et al 2021)

Summary

Medical cannabinoids represent an important adjunctive option for patients experiencing persistent and troubling symptoms of DPNP, and increasingly are listed as a third-line treatment option for neuropathic pain. Both prescription and authorized products are available in Canada, although currently, CBD-dominant options are only available via authorization. Further research is required to more clearly elucidate optimal delivery options, strains and THC:CBD ratios, dosing, and long-term safety data.

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