Navigating cannabinoid choices for chronic neuropathic pain in older adults

Potholes and highlights

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Approximately 18% of Canadian adults use cannabis, which has increased from 14% since the legalization of recreational marijuana.[1] However, less than 2% of Canadians are registered medical cannabis users.[2,3] Chronic pain is a common reason for using cannabis.[4,5] Because neuropathic pain, a subset of chronic pain, affects approximately 8% of patients and is challenging for physicians and patients to manage adequately, an understanding of cannabinoid therapies (ie, prescription cannabinoids or cannabis) is important (**Box 1**).[6-9] This article will review the evidence for cannabinoids in refractory neuropathic pain and highlight tools to assist family physicians who seek practical guidance in advising, authorizing, prescribing, and monitoring cannabinoids. We acknowledge that there are various viewpoints on the role of cannabinoids and we offer multiple considerations.

Case description: Mr Wilson

Mr Wilson, an 81-year-old who lives independently with his wife, has been a patient of yours for a long time. Three weeks ago he had an emergency department (ED) visit owing to dizziness and a near fall, and was told to follow up with his family physician if he continued to feel dizzy.

Box 1. Overview and definitions

The following provides an overview of relevant terminology

- *Cannabinoid:* Any compound that activates a cannabinoid receptor (eg, prescription cannabinoid and cannabis). The most studied, although still poorly understood, are THC and CBD
- *Cannabinoid receptors:* CB_1 receptors (primarily in the central and peripheral nervous system) and CB_2 receptors (primarily in the immune system) are part of the endocannabinoid system
- *Prescription cannabinoids:* Nabilone or nabiximols (see **Table 1**[9] for details)
- *Cannabis:* Marijuana; available legally from a licensed producer or licensed retailer
- *Licensed producer:* Regulated by Health Canada; requires prescribers to authorize medical cannabis via a medical document
- *Licensed retailer:* A regulated retailer or licensed dispensary; regulated by each province and territory, as government-operated, privately licensed stores, or online. Medical oversight is not required

CBD—cannabidiol, THC—tetrahydrocannabinol.

His medical history includes neuropathic pain secondary to long-standing type 2 diabetes mellitus, spinal osteoarthritis, and chronic insomnia. He is an ex-smoker. The discharge summary indicates that findings of the computed tomography scan of his brain were normal and that laboratory test results revealed that complete blood count, renal panel findings, extended electrolyte levels, and random blood glucose level were within normal range. His recent hemoglobin A_{1c} measurement was 7.5%. His blood pressure was 128/84 mm Hg, with no orthostatic drop, and his heart rate was 72 beats/min. Neurologic and cardiac assessments were done, and no evidence of underlying disease was found. Findings of Dix-Hallpike maneuvers were negative.

According to your records, Mr Wilson is currently taking 75 mg of pregabalin twice daily, 60 mg of duloxetine daily, 850 mg of metformin twice daily, 40 units of insulin glargine at night, 20 mg of rosuvastatin daily, 5 mg of ramipril daily, 7.5 mg of zopiclone at night as required (2 or 3 times per week), and 1000 units of vitamin D daily. You recall that nortriptyline was trialed without success a few years ago (it had caused drowsiness and constipation at a dose of 100 mg at night), but after he was switched to pregabalin, Mr Wilson reported some improvement. About a year ago, duloxetine was added, and Mr Wilson reported further improvements in his diabetic neuropathy. Furthermore, Mr Wilson has previously expressed that he wants to avoid opioids "at all costs."

Mr Wilson is still experiencing dizziness, and on today's examination, his blood pressure and heart rate are 120/70 mm Hg and 68 beats/min, respectively, with no orthostasis. You confirm his current medication regimen, with no changes made over the past several months. However, upon routine cannabinoid screening, you discover that Mr Wilson was given cannabidiol (CBD) oil 3 months ago by his son to try to help with his nerve pain. You ask Mr Wilson to complete a Cannabis Use Disorder Identification Test–Revised (**https://bpac.org.nz/BPJ/2010/June/docs/addiction_CUDIT-R.pdf**), on which he scores 4, indicating no hazardous cannabis use.[10]

Importance of cannabinoid screening

Screening for cannabinoid use, even in older adults, is important given the prevalence of cannabis use. Patients

Table 1. Comparison of cannabinoids for treating neuropathic pain: *The full version of the RxFiles cannabinoid treatment chart is available online from CFPlus.

TREATMENT	DOSING (COST)	COMMENTS†
Nabilone	0.25-0.5 mg at night; increase by 0.5-1 mg every 1-2 wk, as tolerated (usual dose of 1 mg twice daily; $112/30 d)	• Capsule that contains a THC analogue (various strengths available) and no CBD • Prescription cannabinoid available from pharmacies. Potential drug coverage by private insurance; not covered by most public insurers for neuropathic pain (eg, provincial, NIHB) • Health Canada indication is for severe chemotherapy-induced nausea and vomiting • Preferred over cannabis for the treatment of chronic neuropathic pain; however, this is an off-label indication[9]
Nabiximols	1 spray at night, increase by 1-2 sprays every 1-2 wk as tolerated (usual dose of 1 spray every 4 h; $504/30 d)	• Sublingual or buccal spray that contains 2.7 mg of THC and 2.5 mg of CBD per spray • Prescription cannabinoid available from pharmacies. Potential drug coverage by private insurance; not covered by most public insurers for neuropathic pain (eg, provincial, NIHB) • Health Canada indication is for the adjunctive treatment of advanced cancer pain and MS neuropathic pain or spasticity • Preferred over cannabis for the treatment of chronic neuropathic pain; however, this is an off-label indication for non-MS neuropathic pain[9]
Cannabis		
• oral cannabis oil • oral cannabis capsules	Unknown. Consider a product with a similar ratio to nabiximols (ie, 1:1 THC:CBD). An example dose might be 2-3 mg of 1:1 THC:CBD at night (60-mL bottle containing 600 mg of THC and 600 mg of CBD is about $160)	• Contains more than 400 compounds including 120 cannabinoids and is marketed based on CBD and THC components • Available from licensed producers or licensed retailers, and some patients might still access it via illicit sources • Licensed producer: Potential drug coverage through private insurance (eg, Manulife, Sun Life) and Veterans Affairs; not covered by public insurers (eg, provincial, NIHB), but patients may claim it on their income tax return • Licensed retailer: No drug coverage available; patients are unable to claim it on their income tax return • No official indication. May be medically authorized in Canada to any patient
• inhaled dried cannabis	Not recommended owing to harms	• In Saskatchewan, when authorizing cannabis, a treatment agreement signed by the patient is required (might not be required in some jurisdictions)

CAGE-AID—CAGE (cut down, annoyed, guilty, eye-opener) Adapted to Include Drugs, CBD—cannabidiol, CUDIT-R—Cannabis Use Disorder Identification Test–Revised, MS—multiple sclerosis, NIHB—Non-Insured Health Benefits, THC—tetrahydrocannabinol.
*The **RxFiles Cannabinoid Drug Comparison Chart** is available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.
†Before prescribing or authorizing, consider screening for hazardous cannabis use or addiction risk using the CUDIT-R, CAGE-AID, or Opioid Risk Tool.

might contemplate self-medicating with cannabis for various reasons, including viewing cannabis as a "natural" (and therefore "safe") alternative, or for managing medical conditions not adequately controlled by their current drug therapy.[9] Prescription cannabinoids (ie, nabiximols and nabilone), when dispensed by a community pharmacy, are captured by provincial or territorial electronic prescription databases. Cannabis is not captured by these databases, which makes it easy to miss unless it is specifically asked about, as was the case with Mr Wilson. When screening, it might be helpful to ask patients separately about medical and recreational (or nonmedical) cannabis or marijuana. Also, prompting patients by asking about specific products such as "CBD oil" or "topical cannabis" might be useful, as these products are not always viewed as medications by patients.

Back to Mr Wilson

Physician: I'm sorry that your nerve pain is still causing problems. I didn't realize how much it was bothering you. Thank you for sharing about your CBD oil though, as it is helpful for your assessment. Did you bring the CBD oil with you?

Mr Wilson: I have a picture of it on my phone. It's really helping me. I started at 1 drop at night and now I take 16 drops. I think my son said it was safe to go up to 40 drops, but I didn't need that much. He picked this one because it just has CBD in it. (The label reads CBD 100 mg/mL.)

Physician: May I make a suggestion about what I think could be the possible cause of your dizziness? [Mr Wilson nods.] I'm concerned that this CBD oil might be contributing to this.

Mr Wilson: But I thought CBD is safe because it doesn't get you high.

Bringing evidence to practice: cannabinoid adverse effects

Cannabinoids can cause many adverse effects that are often underappreciated by patients or their families, such as with Mr Wilson and his son (**Table 2**).[9] Most cannabinoid trials enrol experienced users and exclude older adults and those with comorbidities common among aging patients.[11,12] Interestingly, the risk of adverse effects might even be higher in older adults owing to greater cannabinoid exposure (eg, slower

Table 2. Adverse effects of cannabinoids to assess or monitor

ADVERSE EFFECT	CANNABINOID EVENT RATE, %	PLACEBO EVENT RATE, %	NUMBER NEEDED TO HARM
Overall adverse effects	81	62	6
Withdrawal due to adverse effects	11	Approximately 3	14
"Feeling high"	35	3	4
Sedation	50	30	5
Dizziness	32	11	5
Speech disorders	32	7	5
Ataxia or muscle twitching	30	11	6
Hypotension	25	11	8

Data from Allan et al.[9]

cannabis metabolism and increased fat tissue) compared with younger adults.[11] Cannabis also appears to increase the risk of ED visits. A survey of 14 715 individuals aged 50 years or older found that 30.9% of cannabis users visited the ED compared with 23.5% of nonusers ($P<.001$).[13] Patients, especially older adults, are at risk of cannabinoid-related adverse effects and should be educated about and monitored for these effects.

Cannabinoid therapies can cause dizziness. A systematic review found 3 systematic reviews of cannabinoids versus placebo assessing this adverse effect.[12] The largest systematic review included 41 randomized controlled trials (RCTs) comprising 4243 participants and found an increased risk of dizziness (odds ratio of 5.09, 95% CI 4.10 to 6.32).[14] Increased dizziness with cannabinoid therapy was also found by Wade et al (3 RCTs including 666 participants; 32% vs 11% experienced dizziness; number needed to harm of 5) and by Mücke et al (4 RCTs including 823 patients), who found a numerical, although not statistical, increase in dizziness (risk difference of 3%, 95% CI -2% to 8%).[15,16] Furthermore, cannabinoid therapy is active in the central nervous system (CNS) and it can interact with other CNS-active drugs. The American Geriatric Society Beers criteria recommend avoiding the use of 3 or more CNS-active drugs.[17] Mr Wilson is currently taking 4 CNS-active drugs (ie, pregabalin, zopiclone, duloxetine, cannabis oil), which increases his risk of harm, including dizziness.

Whether CBD alone causes dizziness is unstudied; however, all cannabis oil purchased from a legal source in Canada (ie, licensed producers or licensed retailers) will provide labeled concentrations for both CBD and tetrahydrocannabinol (THC) (see **Box 2** for cannabis oil considerations).[18] Therefore, it is likely that Mr Wilson was given illegal cannabis oil, as the label only listed the concentration for CBD, and that Mr Wilson's cannabis oil does contain an unspecified amount of THC despite no labeled concentration. In addition, products purchased from a legal source will have an excise stamp on the packaging and a standardized cannabis symbol (if the product contains greater than 10 µg of THC per gram), which can be another clue about the source of cannabis.[19,20] To date, all legal cannabis products in Canada contain both CBD and THC.

Back to Mr Wilson

Physician: There really is no such thing as a safe type of cannabis. In fact, about 1 in 5 patients taking a cannabinoid medication will become dizzy. I am especially concerned when the cannabis is combined with your other medications that put you at risk of falling.

Mr Wilson: So, you want me to stop the CBD oil? But, won't my pain come back? I don't feel very good about that.

Bringing evidence to practice: diabetic neuropathic pain management and cannabinoid therapy

Before considering cannabinoid therapy, it is important to discuss goals of therapy with Mr Wilson and assess his previous medication trials. An understanding of Mr Wilson's perceived benefit with cannabis oil is essential. Focusing on functional goals—that is, goals where success is measured by improvements in activities of daily life (eg, ability to play with grandchildren, garden, get groceries)—versus relying solely on pain scores is central to managing chronic pain.[6,21] It is also important to set realistic expectations regarding benefits

Box 2. Cannabis oil considerations

Most patients will report cannabis oil dose in drops or millilitres per day. However, it is important to know the milligram dose of CBD and THC. The concentration (ie, mg/mL) of CBD and THC should be reported on the product's label

- Cannabis dose calculation using Mr Wilson as an example:
  - -Cannabis oil bottle label reads CBD 100 mg/mL; THC concentration is not reported
  - -Mr Wilson is taking 16 drops per day, which is about 0.8 mL/d (rule of thumb: approximately 20 drops per mL)
  - -Mr Wilson is taking approximately 80 mg of CBD per day

CBD—cannabidiol, THC—tetrahydrocannabinol

that can be achieved pharmacologically. For example, a 30% or 50% reduction in pain are common efficacy outcomes assessed in chronic pain RCTs to indicate success; however, some patients might believe that drug therapy will reduce their pain to zero. Because Mr Wilson reported some improvement with both pregabalin and duloxetine, but still pursued self-medicating with cannabis, it would be worthwhile to discuss and set functional goals while emphasizing that complete elimination of pain is unrealistic. In addition, even for patients who might feel as though they have "tried everything," there is often still an opportunity to optimize therapies. Guidelines recommend nonpharmacologic treatment such as exercise, physiotherapy, and psychological therapies in all patients.[7] Furthermore, many patients perceive a drug therapy to have failed, but have not undergone an adequate trial. For example, most medications need to be titrated to an effective dose and used for at least 6 weeks (and likely 3 months) to realize benefit.[9] Of note, older adults usually require lower doses and slower medication titration than younger adults do (see *Geri-RxFiles* available at **www.RxFiles.ca** for further dosing information).[22]

Currently, cannabinoids are considered a third- or fourth-line treatment alternative for chronic neuropathic pain after patients fail tricyclic antidepressants, gabapentinoids, and selective norepinephrine reuptake inhibitor antidepressants.[7,9] For Mr Wilson, cannabinoids might be a reasonable alternative, as he has trialed nortriptyline, pregabalin, and duloxetine. A 2018 Cochrane meta-analysis of 10 RCTs of patients (1586 participants) experiencing chronic neuropathic pain found that cannabinoids compared with placebo increased the number of patients achieving a 30% or greater reduction in pain with a number needed to treat of 11 (moderate quality of evidence).[23] However, there was no difference in patients with diabetic neuropathy based on a subgroup analysis of 2 RCTs (327 participants).[23] In addition, the review attempted to meta-analyze a functional outcome—patient reported global impression of pain—but the quality of evidence was low and further study is required.[23]

Although cannabinoids have been studied in chronic neuropathic pain as outlined above, important limitations exist. Most RCTs included fewer than 100 participants (range 20 to 339), between the ages of approximately 25 to 60 years (up to 70 years), and assessed the prescription cannabinoid nabiximols.[23] None of the RCTs assessed cannabis oil.[23] Two RCTs assessed nabilone (but were not included in the meta-analysis).[23] Most RCTs were 12 weeks in duration (up to 26 weeks), and long-term benefit is unknown.[23] This was further assessed in a systematic review by Allan et al, in which short RCTs (up to 5 weeks) found positive results and longer RCTs (9 to 15 weeks) found neutral results.[12] Thus, cannabinoid effects, especially long-term, remain unknown in older adults, such as Mr Wilson.

Potential management approaches for Mr Wilson

Managing refractory chronic neuropathic pain is challenging; however, there are a few interventions that Mr Wilson would likely benefit from. Goals of care, with an emphasis on function, should be discussed, and Mr Wilson should be reminded that drug therapy is unlikely to reduce his pain level to zero. Nonpharmacologic therapy is helpful and should be explored (eg, psychotherapy, physiotherapy, supervised activity program). An outline of many nonpharmacologic therapies is available online at **www.RxFiles.ca/painlinks**.

Various drug therapy approaches for refractory chronic neuropathic pain are reasonable and depend on many variables such as patient characteristics and values. For Mr Wilson, it might be reasonable to trial an increased dose of either 90 mg of duloxetine daily or 75 mg of pregabalin in the morning and 150 mg at night for 3 months while weighing the potential for benefits and adverse effects.[24,25]

Given that Mr Wilson's cannabis oil is likely illicit and associated with the onset of his dizziness, he should be encouraged to stop using it, or at least to decrease the dose (although it is important to note that Mr Wilson might not follow medical advice). Tapering is advised when stopping, as withdrawal symptoms (eg, anxiety, sweating, and sleep disturbances) have been reported when cannabinoids are used daily for a few weeks to months.[26] While the optimal tapering regimen is unknown, in non-frail elderly patients like Mr Wilson, decreasing the dose by 25% every 1 to 2 weeks as tolerated is reasonable while monitoring for dizziness resolution, cannabis withdrawal symptoms, and effects on function.[27] You might choose to provide Mr Wilson with a cannabis patient booklet, which highlights some cannabis myths and adverse effects (available at **www.RxFiles.ca**).[28]

If alternative cannabinoid therapy is explored (see **Table 1** for cannabinoid product details[9] and the full version of the RxFiles cannabinoid treatment chart available online from **CFPlus***), Mr Wilson should likely be titrated off or given a reduced dose of duloxetine or pregabalin to minimize additive CNS adverse effects.[9] Prescription cannabinoids are preferred over cannabis, as most RCTs assessed these products, dosing guidance is available, provincial and territorial electronic prescription databases capture these products aiding in cannabinoid screening, and the products meet prescription-level quality standards. However, cost might be prohibitive, especially with nabiximols. It would be important to initiate the cannabinoid at a low dose and increase it every few days or weekly, and a reasonable trial duration would be approximately 3 months. In general, the best approach will be patient-centred.

*The **RxFiles Cannabinoid Drug Comparison Chart** is available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Conclusion

Overall, there are many unknowns and uncertainties about the optimal role of cannabinoids in older adults for refractory neuropathic pain. Until more robust data are available, ensure other nonpharmacologic and pharmacologic therapies are optimized and that patients have failed at least 3 other agents before initiating cannabinoid therapy. Patients might be curious and want to explore cannabinoid therapy, so it is important to screen for cannabinoid use, monitor for potential adverse effects, and engage with patients. In addition, cannabinoid-related tools for practice exist to assist family physicians who seek practical guidance for delivering patient care.

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Acknowledgment

We thank **Lynette Kosar** and **Loren Regier** for their review of this article.

Competing interests

RxFiles and contributing authors do not have any commercial competing interests. RxFiles Academic Detailing Program is funded through a grant from Saskatchewan Health to the University of Saskatchewan; additional "not for profit; not for loss" revenue is obtained from sales of books and online subscriptions. No financial assistance was obtained for this publication.

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